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TOBACCO-RELATED DISEASE RESEARCH PROGRAM

Annual Report to the State of California Legislature 1991

University of California
Office of Health Affairs

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Report prepared by University of California
Office of Vice President – Health Affairs

Tobacco-Related Disease Research Program

Cornelius L. Hopper, M.D.
Vice President– Health Affairs

Charles L. Gruder,. Ph.D.
Director

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EXECUTIVE SUMMARY

- During 1991 the University of California Tobacco-Related Disease Research Program (TRDRP) entered its third year of operation. Research supported by grants awarded in the first two annual funding cycles has already yielded important findings which have been reported in scientific publications and at scientific conferences.

- In the second funding cycle, 97 grants for a total of $25,832,810 were awarded to investigators at 29 public and private nonprofit institutions in California.

- In all, investigators at 37 California institutions are currently conducting research on tobacco-related disease with the support of 281 grants for a total of $91,844,625.

- Eight areas in tobacco-related disease research have been identified as priorities for the third funding cycle: cancer; cardiovascular and cerebrovascular disease; pulmonary disease; genetic markers for susceptibility to tobacco-related diseases; nicotine addiction; environmental tobacco smoke; prevention and cessation of tobacco use; and tobacco control. These priority areas were adopted after extensive consultation with many experts and TRDRP constituencies.

- The first progress reports (for the period July 1, 1990 to June 30, 1991) from investigators who received grants in the first cycle revealed that the results of TRDRP-supported research are appearing in the scientific literature: 114 articles and chapters are being published in books and refereed scientific journals, some of which include **Cancer Research, Journal of Biological Chemistry, Journal of Physiology (London), American Review of Respiratory Disease,** and **American Journal of Public Health.** One article, which appeared in the influential **Journal of the American Medical Association,** was singled out for special notice in an editorial in the same issue of the Journal by the Secretary of Health and Human Services, Louis W. Sullivan, M.D.

- Some of the research results thus far:

  Demonstrations of specific biological effects of nicotine and other tobacco products on fetal mortality, blood vessels, blood cells, heart, lung, immune system, and chromosomes.

  Discoveries about the immune response to cancerous lung tumors, and promising new drug treatments for this disease.

  Findings that more than one in five deaths of Californians 35 years of age and older are attributable to smoking, and that adolescent females who smoke also engage in other high-risk health behaviors.

  Demonstration of effects of reduced oxygen on the body's use of fuel.

- TRDRP has maintained regular contact with the Tobacco Control Section of the California Department of Health Services, which is administering the tobacco education, prevention, and cessation programs funded by the Proposition 99 Health Education Account, to ensure that the results of research on tobacco-related disease are available to inform the development of services.

- In the lead editorial in the January, 1992 issue of the **American Journal of Public Health,** the TRDRP has been characterized as an "exemplary" program and recommended as a model for a national program of coordinated federal funding for research on smoking.

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INTRODUCTION

The Tobacco-Related Disease Research Program (TRDRP) allocates funds for research on the causes, prevention, and treatment of tobacco-related disease in California. The funds derive from a surtax on cigarettes and other tobacco products established by Proposition 99, The Tobacco Tax and Health Protection act of 1988, and the ensuing enabling legislation. SB 1613, passed in 1989, requested the University of California to establish this research program with the Research Account created by Proposition 99. The guidelines that govern the program are embodied in Article 8.7 of the California Health and Safety Code.

SECTION 2 of Article 8.7 requests the University of California to report to the Legislature annually on the status of the research program. This is the second annual report. The Overview presents the current status of the program, including the number and dollar amounts of grants awarded in each annual funding cycle and a sample of research findings to date. The second section of this report contains detailed information regarding the eight aspects of the research program as specified in the Statute. This information includes data on grants for each recipient institution and progress reports, including a bibliography of publications, for each project that completed its first year in 1991. The report also includes rosters of the TRDRP Scientific Advisory Committee, committees of expert scientists who conducted the peer reviews of grant applications, and the TRDRP staff.

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OVERVIEW

Background

Proposition 99. In November 1988, voters in the State of California approved an increase in the tax on cigarettes of $0.25 per pack and an equivalent amount for other tobacco products. Collection of the tax began on January 1, 1989, and approximately $600 million was generated in the first year. Five separate accounts were established under the terms of the ballot initiative, Proposition 99, the Tobacco Tax and Health Protection Act of 1988: the Research Account, the Hospital Services Account, the Physician Services Account, the Educational Account, and the Public Resources Account.

Tobacco-Related Disease Research Program. Five percent of the revenue was allocated to the **Research Account,** to fund research on all aspects of tobacco-related diseases in California. The California legislature assigned responsibility for administering the Research Account to the University of California. Within the Office of the President of the University of California, specific responsibility for managing these research funds was given to the Vice President—Health Affairs, Cornelius L. Hopper, M.D., who established the **Tobacco-Related Disease Research Program** (TRDRP). TRDRP has responsibility for the management of all fiscal and programmatic aspects of the grant program, while the Research Administration Office of the Office of the President manages contractual relationships with the institutions receiving grants.

During 1991, a financial audit of TRDRP by the University of California Auditor revealed that the Program has been operating in accord with the legislative mandate and the University's procedures.

Scientific Advisory Committee. A Scientific Advisory Committee advises Vice President Hopper concerning the direction and oversight of TRDRP. The Committee meets quarterly. Initially, members of this committee were drawn from the California affiliates of the American Lung Association, the American Heart Association, and the American Cancer Society; the California Medical Association; private research universities—Stanford University, the University of Southern California, and the California Institute of Technology; and public universities—the California State University and the University of California. In 1991, Vice President Hopper appointed representatives from Lawrence Berkeley Laboratory and Charles R. Drew University of Medicine and Science. All members of the Scientific Advisory Committee are listed in Section 5 below.

Grants Awarded. To date TRDRP has completed two annual funding cycles, 1990 and 1991. Currently, investigators at 37 California institutions are pursuing research on tobacco-related disease with the support of 281 grants for a total of $91,844,625. Most applications requested multi-year funding (the maximum duration is three years) and the full amount awarded for the entire duration has been set aside from funds available in each cycle; in this way, uncertainty about funding for future years is avoided.

The 281 grants are distributed among four types of award as follows:

182 **Research Project** grants to experienced investigators for fully-developed research proposals based on sound theory and strong preliminary evidence.

16 **Innovative Developmental and Exploratory Awards (IDEAs)** for preliminary studies to gather evidence regarding the feasibility of very promising ideas.

49 **New Investigator** Awards to scientists who are beginning research careers as independent investigators.

34 **Postdoctoral Fellowship** Awards to investigators who are obtaining advanced training in fields relevant to tobacco-related disease.

Table 1 displays the number and dollar amount of all awards made by TRDRP to date, broken down by substantive area and recipient institution. It includes four grants which were resigned by the Principal Investigators at the end of the first year, and one which is completed.

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Table 1

ALL TRDRP AWARDS TO DATE BY INSTITUTION AND SUBJECT AREA

The first number under each subject area represents the $ amount and the second number represents the # of awards

Institution	Area of Investigation								
	Cancer	Cardiovascular	Epidemiology	Engineering	Gen Biomedical	Intervention	Public Health, Public Policy	Pulmonary	Total / Institution
ASIAN AMER HLTH FOR		153,533 1							153,533 1
CAL PUB HLTH FOUND		1,322,475 2				627,587 1			1,950,062 3
CAL TECH		191,398 1			643,640 2				835,038 3
CEDARS SINAI					332,966 1			811,536 2	1,144,502 3
CHARLES DREW U						323,095 1			323,095 1
CHILD HOSP, LA		850,235 2						537,909 1	1,388,144 3
CHILD HOSP, OAKL								232,350 1	232,350 1
CHILD HOSP, SF			291,226 1						291,226 1
CITY OF HOPE		432,032 2							432,032 2
KAISER FOUND RES INST					812,645 1				812,645 1
LA JOLLA RES INST	1,196,615 4				75,600 1				1,272,215 5
LB FOUND, VAMC		186,945 1	186,945 1						186,945 1
LBL	225,000 1	333,018 1			768,510 2			417,585 1	1,744,113 5
LLNL					344,430 1				344,430 1
LOMA LINDA U			121,461 1			377,968 1			499,429 2
MARCH OF DIMES			1,287,994 2						1,287,994 2
NCIRE		75,600 1				85,583 1		340,016 1	501,199 3
PA MED FDN RES INST				325,994 1					325,994 1
PUB HLTH FOUND, LA			524,044 1						524,044 1
RAND CORP							407,225 2		407,225 2
REI					458,763 1			451,200 3	909,963 4
SALK INST					1,208,002 3				1,208,002 3
SAN DIEGO STATE U		447,480 1				4,039,499 4	590,850 1		5,077,829 6
SCRIPPS	385,249 2	473,053 2			1,915,876 4			540,380 1	3,314,558 9
SRI INTERN	152,412 1	1,304,098 2		706,185 2	385,657 1				2,548,352 6
STANFORD U	110,646 2	1,167,474 2	455,271 1		665,400 2	1,933,755 4	1,055,960 1	348,150 1	5,736,656 13
UC, BERKELEY	380,159 1		330,068 1		345,357 3		1,416,466 4	1,218,980 3	3,691,030 12
UC, DAVIS	939,994 5	1,011,358 7	658,818 2					1,955,009 9	4,565,179 23
UC, IRVINE	443,601 2		214,066 1	103,468 1	744,534 2		72,837 1	2,174,846 5	3,753,352 12
UC, LOS ANGELES	4,915,871 16	837,757 3	327,439 2	192,878 1	602,795 3	75,000 1	1,267,853 5	878,582 4	9,098,175 35
UC, RIVERSIDE				747,863 3				301,620 1	1,049,483 4
UC, SAN DIEGO	1,376,132 6	335,990 2	621,216 5		2,638,474 13		579,489 1	1,598,693 9	7,149,994 36
UC, SAN FRANCISCO	1,199,843 4	1,681,643 8	3,322,125 6		1,900,215 11	3,061,337 7	3,990,605 11	1,754,633 6	16,910,401 53
UC, SANTA CRUZ	122,082 1								122,082 1
USC	2,901,893 8	1,382,662 3	3,104,476 5		1,377,081 2	2,848,669 4	462,095 1	283,027 1	12,359,903 24
VAMC RES FOUND, SD	291,601 1								291,601 1
WEST CONS PUB HLTH		63,805 1					151,607 1		215,412 2
TOTAL/SUBJ	15,631,764 57	9,533,132 34	12,273,973 31	1,164,820 4	15,457,255 56	14,130,153 26	10,962,590 30	13,504,500 48	92,658,187 286

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First Grant Cycle

In the first funding cycle, 1989-90, researchers at 81 institutions submitted 883 applications requesting $352,935,374. After peer review, grants were awarded to and accepted by 189 investigators at 35 institutions for a total of $67,940,738. Since these awards were made, four investigators resigned their awards and one completed his project, leaving 184 grants in effect for a total of $66,825,377.

The first annual progress reports on these grants were submitted during 1991. Abstracts can be found in Section 3 with the summaries of the grants to each recipient institution. Principal Investigators reported publishing 114 articles, chapters, and monographs, and presenting 14 papers at scientific conferences. A complete bibliography appears in Section 4.

Papers have been presented at numerous scientific meetings, some of which are the First International Conference on Smokeless Tobacco (Payton Jacob, III, Ph.D., University of California, San Francisco; Margaret M. Walsh, Ph.D., Stanford University), the American Academy of Neurology (Roy Halliday, Ph.D., Northern California Institute for Research and Education), and the American Association for Aerosol Research (William W. Nazaroff, Ph.D., University of California, Berkeley).

Articles have been published (or will appear) in many refereed scientific journals, some of which are **Cancer Research** (Alexander Lewis, Ph.D., Stanford University); **Hypertension** (Victor J. Dzau, M.D. Stanford University); **Circulation** (Christopher Glembotski, Ph.D., San Diego State University; Brian A. Cason, M.D., University of California, San Francisco); **Journal of Biological Chemistry** (Joan Heller Brown, Ph.D., University of California, San Diego); **Journal of Physiology (London)** (Stephen F. Heinemann, Ph.D., Salk Institute for Biological Studies); **American Review of Respiratory Disease** (Steven M. Dubinett, M.D., UCLA); and the **American Journal of Public Health** (Miriam Shipp, M.D., M.P.H. and Mary Croughan-Minihane, Ph.D., University of California, San Francisco).

One article, which appeared in the influential Journal of the American Medical Association, was singled out for special notice in an editorial in the same issue of the Journal by the Secretary of Health and Human Services, Louis W. Sullivan, M.D. Secretary Sullivan commended the authors "for their outstanding contribution to the continuing discussion of 'tobacco politics.'" The article, written by TRDRP Principal Investigator, Stanton A. Glantz, Ph.D. of the University of California, San Francisco, and a colleague, reported on the political battle that ensued when Los Angeles attempted to pass tobacco control legislation.

The following are summaries of some notable findings in the various areas.

Cancer

- Benzene, which is found in relatively high concentrations in cigarette smoke, is known to be a cause of leukemia in humans and may, therefore, contribute to an increased incidence of leukemia in smokers. To date, studies with animals have shown that exposure to benzene results in abnormal numbers of chromosomes in micronuclei-containing red blood cells. This complements the finding that exposure of human white blood cells to a benzene metabolite significantly affects cell growth and division, which also results in abnormal numbers of chromosomes. **[David Eastmond, Ph.D., University of California, Riverside]**
- In this clinical trial, a monoclonal antibody drug, KS1/4-methotrexate, has been tested in different escalating doses in 11 patients with metastatic non-small cell carcinoma of the lung. Four weeks after treatment began, one patient showed a decrease in the size of lung tumors, the disease was stable in six patients, and the disease progressed in the remaining four. All patients showed some degree of toxicity as a result of the treatment. **[Darlene Elias, M.D., Scripps Clinic and Research Foundation]**
- Tumor suppressor genes constrain the unlimited proliferation of normal cells and thereby prevent the growth of cancerous tumors. Mutations in one of the major tumor suppressor genes, p53, have been found in one-third of lung tumors analyzed. Such mutations can alter the ability of p53 genes to carry out their anti-cancer function. **[H. Phillip Koeffler, M.D., University of California, Los Angeles]**

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Cardiovascular disease

- Nicotine decreases the production of an important growth factor, IL-6, which is involved in the local immune response, and alters the function of the endothelial cells lining the blood vessels. These alterations could lead to more pronounced infections and lower blood clotting capabilities. [Florence Hofman, Ph.D., University of Southern California]
- Using an animal model, hearts chronically exposed to nicotine appear to show a surprising increase in sensitivity to adrenalin after nicotine exposure as well as a decrease in one of the heart's intrinsic fuels, glycogen. These changes may make smokers more susceptible to abnormal heartbeat rhythms and sudden death from heart attack. [Keith Lurie, M.D., University of California, San Francisco]
- Certain substances in blood, high density lipoproteins (HDL), appear to protect against atherosclerosis, or hardening of the arteries caused by the deposit of plaque containing cholesterol and lipids in artery walls. Smoking decreases the level of HDL, and in this way may contribute to atherosclerosis. Previous research in this laboratory has identified several types of HDL, and recently found that one of these types is able to remove surplus cholesterol from cells. [John P. Kane, M.D., Ph.D., University of California, San Francisco]

Epidemiology

- More than one in five (21.6%) deaths of Californians aged 35 years and older in 1988 are attributable to smoking, making smoking the second leading cause of death among Californians. There was substantial variation among California counties in the rates of death attributable to smoking, ranging from 14.3% to 36.4%. The primary diseases were lung cancer, ischemic heart disease, and chronic obstructive lung disease. [George A. Kaplan, Ph.D., California Public Health Foundation]
- Data from a large study begun in 1960 revealed that 42% of adolescent girls who smoked report consuming alcoholic beverages once or more per week, whereas only 11% of nonsmoking adolescent girls reported drinking. Also, one in three adolescent girls who smoked had her first pregnancy prior to age 20, compared with only one in ten nonsmoking girls. [Barbara J. van den Berg, M.D., Western Consortium for Public Health]
- There is strong evidence that smoking is a cause of cardiovascular disease, but the biological mechanisms of this disease process are poorly understood. One suggested mechanism is the activity of immunoglobin E (IgE), the antibody to allergens, because smoking has been found to be positively associated with IgE levels, and IgE levels may be elevated in cardiovascular disease. New analyses have revealed, however, that the effect of smoking on cardiovascular disease does not appear to be mediated by IgE. [Michael H. Criqui, M.D., M.P.H., University of California, San Diego]

General biomedical science

- Hemoglobin, a protein in red blood cells that transports oxygen from the lungs, is degraded by tobacco smoke products, which leads to damage of red blood cells and tissues. Novel, sensitive assays have been developed for the detection of hemoglobin oxidation and associated iron release. [Rolf Mehlhorn, Ph.D., Lawrence Berkeley Laboratory]
- Lymphocytes, white blood cells which are important in the immune system, respond to stimulation by nicotine, suggesting a mechanism by which nicotine may interfere with normal immune function. [Martin Kagnoff, M.D., University of California, San Diego]
- When pregnant rats were exposed to high doses of nicotine, the fetuses were approximately 25% smaller, and the rates of stillbirth and mortality were greater than in controls. Brain tissues were smaller and showed significant degeneration in the white matter. [David R. Hinton, M.D., University of Southern California]

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Interventions for tobacco-use prevention and cessation

- According to a preliminary study, heavy smokers (average almost two packs a day) who quit smoking experienced maximum withdrawal symptoms during the first 48 hours after quitting. By 6 months, 55% of preliminary sample subjects had relapsed. All relapsers were women, were older, had lower incomes, had made more attempts to quit previously, and were more addicted. [Marcia Ward, Ph.D., SRI International]
- Difficulty sleeping at night combined with daytime fatigue are two of the most commonly reported symptoms by individuals who stop smoking. Abstaining from smoking before going to sleep at night was associated with more disturbed sleep at night, greater daytime sleepiness, and worse mood. [Michael H. Bonnet, Ph.D. and Richard B. Berry, M.D., Long Beach VA Medical Center]
- In a survey of 1,114 athletes in 17 California colleges, 55% of college baseball players and 26% of college football players reported using smokeless tobacco (ST) more than once in the past month. Prevalence of ST use by race was 45% white, 41% Native American, 36% Latino, 28% Asian, 10% black, and 24% other. Almost half (48%) had begun using ST between the ages of 14 and 17 years of age and 36% began after 17. Seventy-nine percent of users reported that they needed to consider quitting. [Margaret M. Walsh, Ed.D., University of California, San Francisco]

Public health, public policy, social behavior, and economics

- In California in 1988, one out of five adult deaths and one out of 12 pediatric deaths were due to smoking. This represents 9.9 years of potential life lost per smoking-attributable death. A total of 42,177 deaths were attributable to smoking, and about three out of ten (12,213) occurred in Los Angeles. [Dorothy P. Rice, Sc.D. (Hon.), University of California, San Francisco]
- A meta-analysis of research which has evaluated the impact of programs designed to prevent adolescents from becoming regular smokers confirmed that, of four types of programs currently employed, social reinforcement programs are most effective. These programs develop adolescents' abilities to recognize social pressures to smoke and skills to resist these pressures, and often also enhance knowledge of immediate social and physical consequences of smoking. [William H. Bruvold, Ph.D., University of California, Berkeley]
- The Tobacco Surtax established by Proposition 99 in 1989 had an immediate effect in reducing cigarette sales (after adjusting for seasonal variation and trend-related changes). In the first month the tax was in effect, January, 1989, consumption was reduced by 1.97 packs per capita. Notably, this effect declined with time because by December, 1990, the reduction was only .77 packs per capita per month. [Teh-wei Hu, Ph.D., University of California, Berkeley]

Pulmonary disease

- Nicotine prevents the normal functioning of neutrophils, which are white blood cells that play an important role in the immune system. This alteration in neutrophil function may contribute to the damage which occurs in smokers' lungs. [Lester Packer, Ph.D., University of California, Berkeley]
- Tobacco-specific compounds perturb both the levels of the intracellular protective antioxidant glutathione (GSH) and the protective heat shock protein (HSP) 72 in cultured human lung epithelial cells. HSP 72 is a "stress" protein that the cells apparently produce for protective purposes, so such in vitro changes suggest that tobacco exposure may stimulate similar protective compounds in lung cells in vivo. [Corrine Wong, Ph.D., University of California, Irvine]
- Cigarette smoking causes hypoxia, a reduced level of oxygen present in inspired air. Sudden exposure to hypoxia is shown to increase the body's use of fuel (glucose) during prolonged moderate intensity exercise. Once the body is acclimated to hypoxia, increased glucose utilization also occurs during rest, and is greatly elevated during exercise. These effects may be mediated by the sympathetic nervous system. [George A. Brooks, Ph.D., University of California, Berkeley]

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Second Grant Cycle

Application Review. In the second funding cycle, 1990-91, TRDRP received 593 applications from 66 institutions requesting $176,606,546. TRDRP staff determined that 583 applications were eligible to be evaluated for scientific merit by peer review. With the assistance of expert consultants, the remaining 10 applications were deemed not responsive to the Program's goals. The large majority were evaluated by one of the following ten study sections and applications in other fields (e.g., engineering) by written reviews.

Research Project Awards
Cancer
Cardiovascular Disease
Epidemiology
General Biomedical Science
Interventions for Tobacco-Use Prevention and Cessation
Public Health, Public Policy, and Economics
Pulmonary Disease

Career Development Awards
New Investigator Awards - Biomedical Science
Postdoctoral Fellowship Awards - Biomedical Science
Career Development Awards - Sociobehavioral Science

TRDRP recruited 212 expert investigators to serve as members of these study sections or to provide written reviews; more than 98% of these reviewers were from outside California. These study sections met for two-day sessions during March and April, 1991, in San Francisco. Each grant application competed for funding only with grant applications of the same type within the study section in which it was reviewed.

Scientific Advisory Committee. The Scientific Advisory Committee and the Vice President accepted the ranking of the applications by merit scores assigned by the study sections, without exception, and grant funds were awarded strictly on the basis of these merit scores. In those instances in which the study sections made specific recommendations for budget revisions and for funding levels that were different from the applicants' requests, these revised funding recommendations were accepted by the Scientific Advisory Committee and the Vice President—Health Affairs without exception. The Scientific Advisory Committee recommended funding an average of 14.8% (range 13.0% to 15.4%) of the applications in the seven research project study sections and an average of 23.1% in the career development award category.

Grants Awarded. TRDRP awarded $25,832,810 to 97 investigators at 28 institutions. This is approximately the amount available for grants from the revenue that was estimated would accrue from July 1, 1991 to June 30, 1992. These awards are distributed across the four award types as indicated in Table 2 and across the seven subject matter areas as indicated in Table 3.

Table 2
Research Grants Awarded by Award Type
Second Cycle
1991

Award type	No. grants	Total $ awarded	No. institutions
Research Projects	50	19,873,816	21
IDEAs	16	1,524,757	10
New Investigators Postdoctoral Fellowships	16	3,380,424	
	15	1,053,813	9
TOTAL	97	25,832,810	28*

* 28 different institutions received at least one grant. The sum of the numbers of institutions for the four types exceeds 28 because institutions received grants of more than one type.

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Table 3
Research Grants Awarded by Subject Matter Area
Second Cycle
1991

Area	No. grants	Total $ awarded	No. institutions
Cancer	20	4,808,910	10
Cardiovascular	12	3,275,119	8
Engineering	1	344,430	1
Epidemiology	11	2,778,752	8
General Biomedical	22	4,297,600	9
Prevention and Cessation	8	4,912,963	5
Public Health, etc.	9	1,791,765	5
Pulmonary	14	3,623,271	10
TOTAL	97	25,832,810	28*

* 28 different institutions received at least one grant. The sum of the numbers of institutions in the eight areas exceeds 28 because institutions received grants in more than one area.

All grants are listed by recipient institution in Section 3 below. The following is a sample of the grants awarded in the second cycle:

Cancer

- Smoking and Leukemia: A Molecular Genetic Approach. [Judith Gasson, Ph.D., University of California, Los Angeles]
- Involvement of RAS and Krev-1 in Lung Cancer. [Lawrence Quilliam, Ph.D., La Jolla Cancer Research Foundation]
- Novel Hypoxic Cytotoxins to Enhance Lung Cancer Radiotherapy. [Daniel Pollart, Ph.D., SRI International]

Cardiovascular disease:

- Effect of Cigarette Smoke on High Risk Lipoprotein Profiles. [Trudy Forte, Ph.D., Lawrence Berkeley Laboratory]
- Tobacco-Induced Hypoxia: Molecular Genetic Responses. [Laurence Kedes, M.D., University of Southern California]
- Activated Protein C in Smokers' Thrombosis. [Andras Gruber, M.D., Scripps Clinic and Research Foundation]

Epidemiology

- Control of Breathing in Infants of Smoking Mothers. [Kathleen Lewis, M.D., Children's Hospital, San Francisco]
- Modeling U.S. Lung Cancer Death Rates. [David Burns, M.D., University of California, San Diego]
- Smoking as a Risk Factor in the Etiology of Down Syndrome. [Claudine Torfs, Ph.D., March of Dimes Birth Defects Foundation]

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General biomedical science

- Vascular Effects of Nicotine: Effect of Age. [Sue Duckles, Ph.D., University of California, Irvine]
- A Hypothalamic Mechanism of Nicotine Reward and Addiction. [Dennis Rasmussen, Ph.D., University of California, San Diego]
- Nicotine, Tobacco Smoke, and the Blood-Brain Barrier. [Berislav Zlokovic, M.D., Ph.D., University of Southern California]

Interventions for tobacco-use prevention and cessation

- Smoking Cessation in Recovering Alcoholic Persons. [John Martin, Ph.D., San Diego State University]
- Relating Tobacco Access and Consumption among Youth. [Stephen Fortmann, M.D., Stanford University]
- Assessment of Teen Tobacco Use by Primary Care Physicians. [Kathryn Hollenbach, Ph.D., M.P.H., University of California, San Francisco]

Public health, public policy, and economics

- The Cost of Passive Smoking on Children's Health. [Robert Valdez, Ph.D., The Rand Corporation]
- Smoking Ordinances, Passive Smoking and Smoking Cessation. [Joel Moskowitz, Ph.D., Western Consortium for Public Health]
- Factors Affecting Smoking Initiation in Young Latina Women. [Celia Kaplan, Dr.P.H., University of California, Los Angeles]

Pulmonary disease

- Effects of Environmental Tobacco Smoke on Pulmonary Allergy. [Laurel Gershwin, D.V.M., Ph.D., University of California, Davis]
- Steroid Influences in Diaphragm Performance in Emphysema. [Michael Lewis, M.D., Cedars-Sinai Medical Center]
- The Effects of Tobacco Smoke on Airway Mucin mRNA. [Carol Basbaum, Ph.D., University of California, San Francisco]

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Future Directions

Third Grant Cycle

Priority Setting. During the summer of 1991, TRDRP held several meetings with funded principal investigators and representatives of national and state organizations which are involved in tobacco-related disease research. The objective of these meetings was to obtain advice from diverse sources as to the direction the TRDRP should be taking in order to enhance the program's impact. Discussion during the meetings explored a wide range of issues, including the need for basic as well as applied research on the causes, prevention, and treatment of tobacco-related diseases and the identification of potential priority areas in which to stimulate research. Response to the meetings was extremely positive and resulted in the formulation and adoption of priority research areas. These were communicated to potential applicants in both the Call for Applications and the Application Packet itself. They are:

Cancer
Cardiovascular and cerebrovascular disease
Pulmonary disease
Genetic markers for susceptibility to tobacco-related diseases
Nicotine addiction
Environmental tobacco smoke
Prevention and cessation of tobacco use
Tobacco control

Application Process. A third funding cycle was begun in Fall 1991, utilizing the same general format as in the 1990-91 funding cycle. Approximately 2,500 copies of the Call for Applications were widely distributed to individuals and institutions statewide, and informational meetings for potential applicants were held in San Diego, Los Angeles, and Berkeley. The closing date for acceptance of applications is January 15, 1992, with awards to become effective on July 1, 1992. Study Sections are scheduled to meet in March and April, 1992.

Information Dissemination

TRDRP staff will be working with the Scientific Advisory Committee to develop programs to disseminate the findings of TRDRP-supported research. Programs will be developed to address several audiences, including: 1) California investigators conducting research on tobacco-related disease, both those supported by TRDRP and those supported by other sources; 2) science and health reporters in the media; and 3) organizations and individuals involved in the tobacco control effort in California. Mechanisms might include conferences, symposia, and publications.

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Source: https://www.industrydocuments.ucsf.edu/docs/fvf0000

Coordination with the Proposition 99 Health Education Account

TRDRP administers the Proposition 99 Research Account. The staff of TRDRP maintained regular contact during 1991 with the State agencies responsible for administering and overseeing the Proposition 99 Health Education Account. This communication included regular meetings with the staff of the Tobacco Control Section, California Department of Health Services. The purpose of this communication was to enable the staffs of the two agencies to keep abreast of developments in their respective programs, to avoid duplication of effort, to take advantage of available expertise, and to provide input into the development of respective program goals. Several noteworthy steps were taken during the year to further the achievement of these ends:

- TRDRP Director C. L. Gruder served on the Tobacco Education Oversight Committee's (TEOC) Ad Hoc Evaluation Subcommittee, and TRDRP Project Officer F. J. Capell served on the California State Department of Education's Drug, Alcohol, and Tobacco Education (D.A.T.E.) Evaluation Technical Advisory Committee.

- Key staff of the Tobacco Control Section and Department of Health Services, including Chronic Diseases Control Branch Chief D. Bal, Tobacco Control Section Chief D. Niemeyer, and Tobacco Control Section Evaluation Unit Chief M. Johnson, participated in TRDRP-sponsored meetings to identify priority areas for research. TEOC Vice Chairperson L. Breslow also participated in this process, as did many experts in tobacco control who are involved in programs funded by the Health Education Account.

- The TRDRP Application Packet and a Request for Proposals issued by the Tobacco Control Section contained an explanation of the distinctions between the TRDRP and Tobacco Control Section programs and encouraged potential applicants to discuss their projects with the appropriate agency staff members.

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Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

2

Specific Reporting Requirements

SPECIFIC REPORTING REQUIREMENTS

SECTION 2 of Article 8.7 of the California Health and Safety Code requests the University of California to provide information annually regarding eight aspects of the Tobacco-Related Disease Research Program. These eight aspects are listed and the information is provided in this section of the report. SECTION 2 states:

The University of California is requested to provide a report on or before December 31, 1990, and annually thereafter, to the Legislature relating to the research gratns awarded with funds provided for tobacco-related disease research pursuant to Article 8.7 (commencing with Section 424.10) of Chapter 2 of Part 1 of Division 1 of the Health and Safety Code. The report shall provide the following information for each campus and institution that receives grant awards:

a) The number and dollar amounts of research grants, including the amount allocated to indirect costs.
b) The subject of research grants by academic discipline.
c) The relationship between state and federal funding for tobacco research.
d) The relationship between each project and the overall strategy of the research program.
e) A summary of research findings.
f) The number and dollar amounts of research grants that involved the use of animals.
g) The number and species of animals used in research.
h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education."

These items are first addressed in the aggregate for all grants. Then, the information is provided separately for each institution which received one or more awards. For each institution every grant is listed, including the name of the Principal Investigator, the title of the research project, the area of research, the term of the project, and the total dollar amount of the award. Finally, copies of the first annual research progress reports for grants awarded in 1990 are reproduced. It should be noted that item d) is not reported for each project for the reason explained in the report of summary data across all institutions.

2023471066

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

SUMMARY DATA FOR 37 INSTITUTIONS

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

286 $92,658,187

b) The subject of research grants by academic discipline (number of grants in parentheses):

Discipline	Number
Cancer	57
Cardiovascular Diseases	34
Engineering	4
Epidemiology	31
General Biomedical Science	56
Pulmonary Diseases	48
Public Health, Public Policy, and Economics	30
Interventions for Tobacco-Use Prevention and Cessation	26

c) The relationship between State and Federal funding for tobacco research:

Other State	$4,140,184
Federal	$10,649,695

d) The relationship between each project and the overall strategy of the research program:

The overall strategy of the research program is to support research on the causes, prevention, and treatment of tobacco-related disease. The relationship between each project and this overall strategy was determined by assessing the relevance of each project to tobacco-related disease. The Legislature defined tobacco-related disease and tobacco-related disease research as follows in Section 424.30 of the Health and Safety Code:

"(c) 'Tobacco-related disease' includes, but is not limited to, the following:

(1) Coronary heart disease.

(2) Cerebrovascular disease.

(3) Cancer, including cancers of the lung, larynx, esophagus, bladder, pancreas, and mouth.

(4) Chronic obstructive lung disease, including emphysema, chronic bronchitis, asthma, and related lung disorders.

(5) Other conditions or diseases that smoking or tobacco use have been established to be a risk factor for excess disability and illness.

(d) 'Tobacco-related disease research' includes, but is not limited to, research in the fields of biomedical science, the behavioral sciences, epidemiology, and public health."

TRDRP employed the following procedure to decide the relevance of each project to the Program's mandate. TRDRP staff reviewed each application and decided whether the project was clearly relevant or not. Those projects which did not have clear relevance to the program were sent out to relevance reviewers with expertise in the area of research for their opinions on the responsiveness of these applications to Proposition 99. Relevance reviewers were recruited through recommendations from the the Interim Steering Committee and other knowledgable sources in California who were unlikely to have a conflict of interest on the particular application. If at least two out of three relevance reviewers found the application to be relevant, the proposal was assigned to a study section. Otherwise, it was removed from the pool of applications and the applicant notified of the decision. 98.3% of the 593 proposals submitted were deemed relevant to the mandate of the Tobacco-Related Disease Research Program.

2023471067

Source: https://www.industrydocuments.ucsf.edu/docs/fnl0000

e) A summary of research findings:

Copies of the abstracts of research progress reports submitted by Principal Investigators who received grants in the first funding cycle are reproduced in Section 3 below in the reports on individual recipient institutions.

f) The number and dollar amounts of research grants that involved the use of animals:
96 of 286 (33.6%) grants at 23 institutions
$29,363,471 of $92,658,187 (31.7%).

g) The species and number of animals used in research per year:

Species	Number
Chickens	365
Dogs	75
Ferrets	80
Frogs	250
Guinea Pigs	254
Hamsters	910
Horses	10
Mice	6,970
Monkeys	15
Pigs	145
Rabbits	622
Rats	8,988

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's (OTA) 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

74 of 286 (26%) grants
$21,273,324 of 92,658,187 (23%)

The OTA defines "alternatives" as any subjects, protocols, or technologies that "replace the use of laboratory animals altogether, reduce the number of animals required, or redefine existing procedures or techniques as to minimize the level of stress endured by the animal" (OTA Report, p 39). Replacement can refer to techniques that replace laboratory animals with non-living systems, such as computer models; with living systems, such as organs or tissue culture; or with invertebrates instead of vertebrate animals. Reduction means using fewer animals than would have been previously required, through the use of improved statistical methods or the sharing of research animals. Refinement includes alteration of procedures to minimize the discomfort caused to animal subjects such as the use of more effective analgesics or closer monitoring for signs of pain.

Of those projects for which animal models were appropriate, 74/124 (60%) used alternative methods either exclusively or in part. Replacement was the most frequently cited alternative (59%); replacement methods included use of tissues, cell lines, and computer modelling. Reduction, cited for 36% of the projects, included sharing animals with other investigators, using animals as their own controls, purchasing commercially available animal tissues and/or products, and the utilizing improved statistical analyses. Refinement was cited in 5% of projects using alternative methods and included improved monitoring of vital signs, less invasive procedures, and improved surgical techniques.

2023471068

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

Grant Awards by Institution

2023471069

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

3

Grant Awards by Institution

Asian American Health Forum

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
1 $153,533

b) The subject of research grants by academic discipline:
Epidemiology = 1

c) The relationship between State and Federal funding for tobacco research:
Other State = $280,500

d) The relationship between each project and the overall strategy of the research program:
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
0

g) The number and species of animals used in research:
N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
N/A

Grant Recipient(s):

1. Jang, Michael H. *Epidemiology*
Filipino smoking prevalence survey in California
$153,533 (7/90-12/91)

AWARD NO. _____ AWARD YEAR 1 X 2 ___ 3 ___

PRINCIPAL INVESTIGATOR Michael Jang

INSTITUTION Asian American Health Forum

TITLE OF PROJECT Filipino Smoking Prevalence Study

Please summarize, in language understandable to an educated lay person, the objectives of this project and the progress to date toward achievement of the specific aims. Print the abstract in the box.

The Filipino Smoking Prevalence Survey (FSPS) was initiated in California by Asian American Health Forum in 1991. The FSPS is designed to collect information on smoking behaviors of Filipino adult residents and to determine the prevalence of their smoking. The survey also collects information on smoking attitudes and what types of prevention messages would be effective in a media campaign.

The California Filipino sample was drawn from all Filipino households with adults over the age of 18 who have listed telephone numbers and those who have automobiles registered with the State Department of Motor Vehicles. A random sample of the universe was obtained from Survey Sample, a survey sampling firm in Connecticut.

After contacting a Filipino residence, one adult, 18 years of age or older was randomly selected to be interviewed from among all the adults residing in the household. Ringing with no answers and busy signals were called back three times on different days before being replaced.

The questionnaire was pre-tested and include a number of questions which were selected for comparability with the state baseline survey. Standard demographic questions were included. To reflect the cultural diversity of California's Filipino population, questions on acculturation were added to the questionnaire. The questionnaire took about 20 minutes to complete.

The telephone interviews were conducted by Filipino interviewers between January and March of 1991. A sample size of 1,300 was selected to achieve a 95% confidence level and a 3% precision for smoking prevalence estimates for the total Filipino population.

Preliminary data analysis has been completed. In 1991, the proportion of California's Filipino adults who reported current smoking was 13.8%. A much greater percentage of men (20%) than women (6.9%), were smokers. While the trend was found in place of birth, those who were foreign born,(18%), had a higher percentage of smokers.

The analysis is continuing and will be completed by December, 1991. The analysis will focus on the relationship between smoking attitudes and smoking behaviors. Efforts are being made to examine the perception that smoking is a polite social gesture. Other analysis will examine the effectiveness of the California's Smoking Media Campaign in terms of recognition and it's impact on smoking cessation.

Cal

a)

b)

c)

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g)

h)

2023471070

Source: https://www.industrydocuments.ucsf.edu/docs/tvl0000

California Institute of Technology

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
3 $835,038

b) The subject of research grants by academic discipline:
Cardiovascular Diseases = 1
General Biomedical Science = 2

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program:
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
2 $643,640

g) The number and species of animals used in research:
Chicken = 15/year
Frogs = 100/year
Rabbits = 5/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
2 $643,640

Grant Recipient(s):

1. Lazarides, Elias Cardiovascular
Control of differentiation of the early embryonic heart
$191,398 (7/90-6/91)

2. Lester, Henry Gen Biomed
Heterologous expression of brain nicotinic receptors
$586,840 (7/90-6/93)

3. Loo, Seng Gen Biomed
Role of yeast cdc7 gene inhibition of DNA replication
$56,800 (7/91-6/93)

AWARD # 1RO1274 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Elias Lazarides

INSTITUTION California Institute of Technology

TITLE OF PROJECT Control of Differentialton of the early Embryonic Heart

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Congenital defects occur with the greatest frequency in the heart and of these most are attributed to anomalous development of cardiac mesenchyme. Cardiac mesenchyme forms structures essential for proper functioning of the adult heart (e.g., valves and septa). Despite the high incidence of valvular involvement in congenital and acquired diseases, there is a paucity of information about their development and how they contribute to the overall function of the heart both *in utero* and postpartum. Our long-term objective is to discern the mechanisms governing mesenchyme formation in order to provide a manipulative model to study how tissue interactions are mediated during development and ultimately how anomalous development of mesenchyme takes place. Given that heavy smoking during pregnancy has been shown to greatly increase the risk of cardiopulmonary disorders in neonatal infants and maybe an as yet unsuspected causative factor in sudden infant death syndrome (SIDS) induced by apnoea, a strong possibility is that some derivative of tobacco smoke induces anomalous patterns of development in the early heart.

Early cardiac morphogenesis is characterized by the remodeling of a simple tubular structure, consisting of two concentric epithelia separated by a "jelly" into a multichambered, specialized organ. This process is initiated by a regionally specific differentiation of the inner epithelium, the endothelium, to produce the actively migrating mesenchymal cells which invade the "cardiac jelly" and ultimately form the tissue of the septa and valves in the heart. We propose to examine how the endothelial cells differentiate to mesenchymal cells. *In vitro* studies have indicated that mesenchyme production is due to a stimulus produced by the "cardiac jelly" or the ventricular myocardium. Furthermore, a growth factor in combination with an explant of ventricular myocardium stimulates the formation of mesenchyme from endothelium. We will first attempt to identify the chemical nature of the stimulus of the myocardium. Then we will analyze how the growth factor and this stimulus interact in order to stimulate the formation of mesenchyme from endothelium. Our preliminary evidence indicates that this factor is analogous to the growth hormone TGF-B. Molecular identification of endogenous TGF-B and its receptor will permit a molecular analysis of this fundamental aspect of cardiac differentiation and morphogenesis. In addition to their direct contribution to our basic understanding of developmental processes these studies will provide a well defined manipulative model where the effect of environmental factors such as tobacco smoke derivatives on early embryonic morphogenetic processes can be assessed

AWARD # 1RT 365 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Henry A. Lester

INSTITUTION California Institute of Technology

TITLE OF PROJECT Heterologous Expression of Brain Nicotinic Receptors

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Nicotine addiction is one major reason for continued widespread tobacco use. The reinforcing effects of nicotine appear to be mediated primarily by high affinity nicotinic receptors and their activation and inactivation by nicotine. Recent advances in molecular biology have resulted in cDNA clones for brain nicotinic receptors. These clones will be expressed heterologously in *Xenopus* oocytes, making them accessible to a variety of electrophysiological and molecular biological techniques. We intend to use a combination of these techniques to study heterologously-expressed, brain nicotinic receptors. Our research will include: (1) a description of the pharmacology, kinetics, ion-selectivity, and second-messenger regulation of wild-type brain nicotinic receptors, (2) the use of site-directed mutagenesis to explore structure-function relationships of the receptors, and (3) development of a novel heterologous expression system using recombinant vaccinia virus. This new expression system will allow the study of cloned brain nAChRs in mammalian cell lines and will lead to large-scale production of the receptors for purification, crystallization, and structural studies.

3

Grant Awards by Institution

2023471071

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

California Public Health Foundation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

3 $1,950,062

b) The subject of research grants by academic discipline:

Epidemiology = 2
Public Health, Public Policy, and Economics = 1

c) The relationship between State and Federal funding for tobacco research:

Other State = $18,000
Federal = $21,572

d) The relationship between each project and the overall strategy of the research program:

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Austin, Donald F. Epidemiology
Laryngeal cancer risk factors: tobacco interactions
$727,322 (7/90-6/93)

2. Kaplan, George A. Pub Health
Surveillance for tobacco-related diseases
$627,587 (7/90-6/93)

3. Lee, Marion M. Epidemiology
Smoking and passive smoking patterns in Chinese Americans
$595,153 (7/90-6/93)

AWARD # 1RT139 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Donald F. Austin, MD, MPH

INSTITUTION California Public Health Foundation

TITLE OF PROJECT Laryngeal Cancer Risk Factors: Tobacco Interactions

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Tobacco and alcohol are both major risk factors for larynx cancer and evidence exists that dietary factors modify that risk. The risk of developing the disease and the risk of dying from it, however, are not related to these factors in the same way for males and females, nor for Blacks and Whites. Based on our analysis of SEER data, it appears that males tend to get larynx cancer in the glottis subsite, with a relatively good prognosis, while females tend to get the disease in the subglottis, with a relatively poor prognosis. It appears from available data that the risks from smoking, alcohol and dietary factors differ markedly by subsite and the risk of disease in ethnic and gender groups depends upon the interaction of these and other factors. It is not known whether these factors interact differently by sex or whether males and females merely differ in exposure.

This project researches the risk of tobacco and co-factors on larynx cancer by subsite. We expect to establish the relative and attributable risks for major larynx cancer risk factors and account for most of the rate anomalies between males and females and between Blacks and Whites. Approximately 700 cases from all reporting areas have been identified, however only those cases with advanced disease have been targeted for interviewing because portions of the interview have been under revision. Approximately 200 such interviews are completed. Other cases and all control interviews were postponed until the outcome of a comparison project proposal for TRDRP was known. That project was not funded so now the other cases and the control interviews will proceed. All telephone numbers for the RDD control calls have been identified.

AWARD # 1RT482 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR GEORGE A. KAPLAN, PH.D.

INSTITUTION CALIFORNIA PUBLIC HEALTH FOUNDATION

TITLE OF PROJECT SURVEILLANCE FOR TOBACCO-RELATED DISEASES

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Public health measures aimed at reducing the burden of disease in a community must, by necessity, be based on accurate, reliable and timely information concerning the occurrence and distribution of disease and risk factors within that community. Thus, surveillance activities are the cornerstone of public health interventions. This study is conducting surveillance for tobacco-related diseases in California using mortality and hospital discharge information. It is examining both tobacco-related deaths and discharges, those in which tobacco plays some role, and tobacco-attributable deaths and discharges, those which can be directly attributed to tobacco exposure.

Current analyses indicate that in 1988, smoking attributable deaths totaled 42,000. These deaths represented 21.6% of all deaths among Californians aged 35 years or older. Of this total, lung cancer and ischemic heart disease each accounted for approximately 10,000 deaths attributable to smoking, and chronic obstructive lung disease accounted for 7,000. When deaths related to smoking are subtracted from the standard disease groupings, smoking is the second leading cause of death among Californians, second only to non-smoking related disease of the heart. These smoking related deaths resulted in over 400,000 years of life lost prior to age 80, and over $3.8 billion dollars in indirect and direct costs.

Substantial variations in rates of smoking attributable deaths are seen both between and within counties. For example, the percent of total deaths attributable to smoking ranged from 14.3% in Mono County to 36.4% in Mariposa County. When a single county was examined (Alameda) there were substantial variations between zip codes in smoking-attributable mortality. Standardized mortality ratios for smoking attributable deaths, the ratio of the number of observed deaths to that expected based on the age and sex distribution of the zip code, ranged from a low of 0.47 to a high of 1.47. Further investigation will be needed to ascertain the reasons for this variation between and within counties.

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Source: https://www.industrydocuments.ucsf.edu/docs/fbcd0000

AWARD # IRT 501 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Marion M. Lee, Ph.D.

INSTITUTION California Public Health Foundation

TITLE OF PROJECT Smoking and Passive Smoking in Chinese Americans

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The overall objectives of this study are a) to measure the prevalence of smoking and passive smoking, and b) to study the social, cognitive, psychological, and environmental factors relating to smoking behavior among Chinese adults and Chinese youths attending grades 6 through 12.

The project team has been meeting regularly to discuss issues of methodology, and the development of both the adult and youth questionnaire. The adult questionnaire adapted from the California Smoking Baseline Survey has been developed. It has been tested on the telephone and translated into Mandarin and Cantonese. A Cantonese-speaking focus group has been conducted to discuss the feasibility and clarity of the questionnaire items. The focus group participants gave many useful suggestions for the revision of the questionnaire. The revised version of the adult questionnaire is now being tested on the phone. A San Francisco based company Freeman and Sullivan Inc. has been selected to conduct 2,000 telephone interviews during the second year. The Youth questionnaire adapted from the California Baseline Smoking Survey and the Teenage Attitudes and Practices Survey has also been developed. Due to the complexity in obtaining approval from different school districts within each study county, the project team has decided to conduct the survey in schools within the San Francsico Unified School District. The study protocol, the parental consent form and the questionnaire have been submitted to the district school officials for review and approval. An advisory committee consisting of representatives from local Asian health and services organizations and the School District has been formed, the committee members will convene to discuss sampling procedures, and to review the questionnaires.

Grant Awards by Institution

2023471073

Source: https://www.industrydocuments.ucsf.edu/docs/ltvj0000

3

Grant Awards by Institution

Cedars Sinai Medical Center

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

3 $1,144,502

b) The subject of research grants by academic discipline:

General Biomedical Science = 1
Pulmonary Disease = 2

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

1 $343,914

g) The number and species of animals used in research:

Hamsters = 80/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

0

Grant Recipient(s):

1. Belman, Michael J. Pulmonary
Optim. of train. in patients w/chronic obstruc. pulm. disease
$467,622 (7/90-6/93)

2. Castro, Christine Gen Biomed
Tobacco use in pregnancy: chronic effects on blood flow
$332,966 (7/90-6/93)

3. Lewis, Michael Pulmonary
Steroid influences on diaphragm performance in emphysema
$343,914 (7/91-6/94)

AWARD # RR-120 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Michael J. Belman, M.D.

INSTITUTION Cedars-Sinai Medical Center

TITLE OF PROJECT "Optimization of Ventilatory Muscle Training in Patients with Chronic Obstructive Pulmonary Disease"

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Chronic obstructive pulmonary disease (COPD), also known as chronic bronchitis and emphysema, is a common and devastating complication of cigarette smoking. Although the disease primarily affects the lungs, the breathing muscles are secondarily impaired. Training of the breathing muscles can improve their function and may provide additional benefits including an improvement in exercise capacity and a reduction in breathlessness. This study aims to develop guidelines for the most effective methods with which to train the breathing muscles in these patients. We hypothesize that the improvement in breathing muscle performance is related to the method in which they are trained. Our objective therefore, is to train patients with COPD in three different methods of ventilatory breathing muscle training: 1) an unloaded panting maneuver; 2) a panting maneuver against a partial obstruction; and 3) a breathing maneuver against a complete obstruction. Tests of breathing muscle strength and endurance and evaluation of breathlessness will be performed before and after the training. By means of unloaded and loaded breathing circuits, we have defined these breathing muscle loads which will be used for the training. These three loads cover a spectrum from an unloaded panting maneuver which provides a low tension, high repetition activity for the muscle, to a load which provides a high pressure low repetition maneuver. The initial testing of the patients has commenced and the training regimen will start in July, 1991. After completion of the study, our goal is to provide definitive guidelines for the use of breathing muscle retraining in COPD patients.

AWARD # 1KT96 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Lony Christine Castro, M.D.

INSTITUTION: Cedars-Sinai Medical Center/UCLA School of Med.

TITLE OF PROJECT Tobacco Use in Pregnancy: Chronic Effects on Blood Flow

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The goals of this 3 year study are 1) to characterize the chronic effects of cigarette smoking during pregnancy on fetal growth and perinatal complications; 2) to evaluate the corresponding changes in placental doppler flow velocity waveforms and those vasoactive hormones known to regulate placental blood flow. In the past year we have standardized the methology for the doppler waveforms in our laboratory as well as the assays for angiotensin II, endothelin -1, atrial natriuretic factor and thromboxane. We have enrolled 44 pregnant women into our study (1/3 of our projected total enrollment). 32 are smokers (S) and 12 are non-smokers (NS). 84% of the S and 66% of the NS have delivered and completed the study. Preliminary Results: There were no differences between S and NS for age, pre-pregnancy weight, education, marital status, preterm labor or preterm rupture of membranes. The frequencies of maternal and neonatal infections were higher in S vs NS (48%vs 0%, p<.001 and 19% vs 0%, p<.01 respectively). Gestational age at delivery was similar in S vs NS (38.3±.5 vs 38.8±.6). Although not statistically significant, birthweight tended to be lower in S vs NS (2905±113 vs 3115±168). Doppler waveform analysis showed that the systolic/diastolic ratio (S/D) and resistance index (RI) declined significantly along the length of the uterine artery in both groups (p<.01). No subject had an abnormal doppler value in the 3rd trimester. Fetal growth curves showed that the biparietal diameter, (BPD), abdominal circumference (AC) and femur length (FL) were above the tenth percentile for our population in both S and NS until 32 weeks. After this time the mean BPD, AC and FL dropped to ≤ 10% in the S only. Conclusions: Although this study is in its early stages and significance has not yet been reached for most findings, the data suggest that the effect of smoking on birthweight is mediated primarily through altered fetal growth, not preterm delivery. The decline in fetal growth occured in the last 8 weeks of pregnancy and was not accompanied by abnormalities in the doppler indices. These findings support earlier epidemiologic studies suggesting that if women stop smoking prior to the third trimester they may be able to avoid the adverse effect on birthweight.

2023471074

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

Charles Drew University of Medicine and Science

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
1 $323,095

b) The subject of research grants by academic discipline:
Tobacco-Use Prevention, Intervention, and Cessation = 1

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program:
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
0

g) The number and species of animals used in research:
N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
N/A

Grant Recipient(s):

1. Davis, Donna T. Intervention
A smoking prevention model for low income minority youth
$323,095 (7/90-6/93)

AWARD # KT35 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Donna T. Davis, Ph.D.

INSTITUTION Charles Drew University of Medicine & Science

TITLE OF PROJECT A Smoking Prevention Model for Low Income Minority Youth

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of the Youth & Smoking Prevention Study is to develop and evaluate a smoking cessation and prevention intervention for African-Americans and Latino youth. The context for the use and evaluation of the intervention is adolescent-focussed health clinics. The long range goal is to design an approach to intervention that would facilitate institutionalization of the intervention in clinics.

Three phases of research are planned. -- Qualitative Study, Intervention Pilot Study and Student Follow-Up Study. Phase I -- Qualitative Study is near completion. The initial assessment of smoking status/behavior, Social Skills, Personal Skills, Social Influences and Personal Attitudes has been completed with 200 youths. Half of the students have participated in the final assessment and data collection with those that remain is in progress.

30

Grant Awards by Institution

2023471075

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

3

Grant Awards by Institution

Childrens Hospital of Los Angeles

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
3 $1,388,144

b) The subject of research grants by academic discipline:
Cancer = 2
Pulmonary Disease = 1

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
1 $346,980

g) The number and species of animals used in research:
Mice = 400/year
Rabbits = 20/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
1 $503,255

Grant Recipient(s):

1. Laug, Walter Cancer
Novel immunotherapy for small cell lung carcinoma
$503,255 (7/90-6/93)

2. T'ang, Anne Cancer
The role of tobacco smoke in multi-step carcinogenesis
$346,980 (7/90-6/93)

3. Torres, Martine Pulmonary
Role of elastin peptides in neutrophil-mediated lung injury
$537,909 (7/91-6/94)

AWARD # RT-74 AWARD PERIOD 7/1/90 to 6/30/91

PRINCIPAL INVESTIGATOR Walter E. Laug, M.D.

INSTITUTION Childrens Hospital Los Angeles

TITLE OF PROJECT Novel Immunotherapy for Small Cell Lung Carcinoma

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The immune system consisting of B and T cells protects against disease causing agents including cancer cells by recognition and subsequent elimination of foreign non-self, antigens. B-cells produce immunoglobulins which bind soluble antigens; e.g., viruses, while T-cells recognize and bind with a special receptor (T-cell receptor) antigens associated with cells (e.g., tumor cells). This recognition is further restricted to antigen-bearing cells which have a second, specific protein called major histocompatibility complex (MHC). All normal cells have MHC protein but many tumor cells lack it, thus evading recognition and destruction by T-cells. We propose to alter with molecular biological methods the T-cell receptor so it can recognize tumor cell antigens independent of MHC proteins.

Immunoglobulins and T-cell receptors have similar structures consisting of two chains of different proteins held together by special bonds. Each of these protein chains has two distinct regions: the variable region which is responsible for recognition and binding to the antigen, and the constant region anchoring the protein chains into the membrane of of B and T-cells, respectively. Since the variable region of the immunoglobulins does not need the presence of MHC proteins for recognition and binding of antigen, we intend to replace the variable region of the T-cell receptor wth the gene coding for the variable region of immunoglobulins. This will result in T-cell receptors recognizing antigens in the absence of MHC proteins. Using genes recognizing specific tumor cell antigens on small-cell lung carcinoma cells, we will obtain receptors which, when transfected into normal T-cells, will recognize and destroy tumor cells. Our project focuses on small-cell lung carcinoma due to its extremely poor prognosis when treated with conventional therapy.

The goal of this proposal, therefore, it to specifically alter in cancer patients their immune system so the patient's own T-cells destroy the tumor. This approach may result in a novel and very specific treatment of cancer.

AWARD # KT108 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Anne T'Ang

INSTITUTION Childrens Hospital of Los Angeles

TITLE OF PROJECT The role of tobacco smoke in multistep carcinogenesis

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The relationship between smoking and the development of certain cancers e.g. lung and bladder carcinomas has long been suspected. However, the exact nature of this relationship is unknown. My hypothesis is that tobacco smoke causes genetic mutations in the lung and bladder cells of heavy smokers. Because cancer is a multistep process, a long time lapse is required before the effect of smoking appears. The aim of this proposal is to reveal the accumulation of cancer predisposing genetic mutations in the target cells of smokers in order to understand the role of chemical carcinogens in the development of cancer. The success of these experiments will give credibility to the clinical and statistical correlation between smoking and cancer at the molecular level. The first year of this project has been spent laying the foundation for future experiments. Preliminary experiments were performed to determine the number of tumor cells necessary to give rise to a tumor, and to show that injection of the same number of normal bladder or lung epithelial cells do not give rise to a tumor. We have shown that at least 10^6 to 10^5 cells have to be injected to form a tumor, and that depending on the aggressiveness of the tumor a time range of 2 - 8 weeks are required for the tumor to form. With this preliminary data in hand, we can now inject cells from the lung or bladder epithelial cells of non-smokers vs. smokers and continue the study as specified in the original proposal.

2023471076

Source: https://www.industrydocuments.ucsf.edu/tobacco/

Childrens Hospital of Oakland

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

1 $232,350

b) The subject of research grants by academic discipline:

Pulmonary Disease = 1

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Bearer, Cynthia F. Pulmonary

Persistent pulmonary hypertension and maternal smoking

$232,350 (7/90-6/92)

AWARD # KT-125 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Cynthia F. Bearer

INSTITUTION Children's Hospital Oakland

TITLE OF PROJECT Persistent Pulmonary Hypertension and Maternal Smoking

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this study is to determine if maternal tobacco smoke exposure is associated with the presence and/or severity of increased pulmonary vascular resistance in the newborn. The study is at the end of the first year and no results are available at this time.

Grant Awards by Institution

2023471077

Source: https://www.industrydocuments.ucsf.edu/docs/lwv0000

3

Grant Awards by Institution

Children's Hospital of San Francisco

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
1 $291,226

b) The subject of research grants by academic discipline:
Epidemiology = 1

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
0

g) The number and species of animals used in research:
N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
N/A

Grant Recipient(s):

1. Lewis, Kathleen Epidemiology
Control of breathing in infants of smoking mothers
$291,226 (7/91-6/93)

2023471078

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

City of Hope National Medical Center

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
2 $432,032

b) The subject of research grants by academic discipline:
Cancer = 2

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
1 $319,776

g) The number and species of animals used in research:
Mice = 110/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
1 $319,776

Grant Recipient(s):

1. Chen, Feng-Ming Cancer
Tumor models & radioimmunotherapy of human lung cancers
$319,776 (7/90-6/93)

2. Termini, John Cancer
Targeting of SCLC myc mRNA by photoactivatable DNA probes
$112,256 (7/91-6/92)

AWARD # IKT 48 AWARD PERIOD July 1, 1990 - June 30, 1993

PRINCIPAL INVESTIGATOR Feng-Ming Chen, Ph.D.

INSTITUTION City of Hope National Medical Center

TITLE OF PROJECT Tumor Models and Radioimmunotherapy of Human Lung Cancers

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this research project is to establish tumor spheroid models and tumor-bearing animal models for testing TNT-1 radioimmunotherapy of human lung cancer. TNT-1 is a murine monoclonal antibody (MAb) directed to the intracellular antigens of degenerating cells. Presumably, this antibody is not uptaken by normal tissue when it is injected intravenously because of the impermeable barrier of the cell membrane. However, many malignant tumors contain a high proportion of dead and dying cells which lose their membrance integrity and enable the TNT MAb to bind to the tumors in a selective manner, killing surrounding viable tumor cells by highly energetic beta-emitting (such as I-131) radiolabeling.

We have now completed the establishment of lung tumor models. These include the in vitro tumor spheroid model (NCI-H460 and NCI-H1437 lung carcinoma cell lines) and in vivo s.c. (subcutaneous), i.v. (intravenous) and i.b. (intrabronchial implantation) models. The tumor growth curve for each model has been investigated. We are now studying the optimization of combined chemotherapy and TNT-1 radioimmunotherapy using the tumor spheroid model. In the s.c. NCI-H460 and NCI-H1437 tumor-bearing nude mice model, we obtained a preliminary result in biodistribution which shows a significant amount of I-125-TNT-1 MAb uptake by the tumors. This s.c. tumor model will be used for further TNT radioimmunoimaging and therapy studies. In the studies of i.v. and i.b. implantation in nude mice models, the tumor colonies were found in the bronchi region (i.b.), the lung (i.b. and i.v.), perioneal cavity (i.v.) and in the liver (i.v.). These two tumor models are ideal metastatic lung tumor models and will be used for the study of different therapeutic modalities using TNT-1 MAb as mentioned above.

While we were establishing the above tumor models, we tested the TNT radioimmunotherapy in an existing tumor spheroid model in our laboratory. In this study, I-131 labeled TNT-1 MAb was used to treat human colon adenocarcinoma HT-29 spheroids. We demonstrated a cascade therapeutic effect when multiple TNT treatments were administrated over time (Effects of ^{131}I-Labeled TNT-1 Radioimmunotherapy on HT-29 Human Colon Adenocarcinoma Spheroids, F.M. Chen, et al., Cancer Immunology Immunotherapy 33:158-168, 1991). This study showed that the therapeutic effects of ^{131}I-TNT-1 depend on radioactive dose, treatment time and number of treatments, and provides valuable information for our ongoing TNT radioimmunotherapy studies in human lung cancer.

3

Grant Awards by Institution

2023471079

Source: https://www.industrydocuments.ucsf.edu/docs/#id=0000

3

Grant Awards by Institution

Kaiser Foundation Research Institute

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

1 $812,645

b) The subject of research grants by academic discipline:

Tobacco-Use Prevention, Intervention, and Cessation = 1

c) The relationship between State and Federal funding for tobacco research:

Other State = 0
Federal = $524,728

d) The relationship between each project and the overall strategy of the research program:

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Corbett, Kitty Intervention
Predictors of weight gain after smoking cessation
$812,645 (7/90-6/93)

AWARD # RT 427 AWARD PERIOD July 1, 1990 - June 30, 1993

PRINCIPAL INVESTIGATOR Kitty Corbett, Ph.D.

INSTITUTION Kaiser Foundation Research Institute

TITLE OF PROJECT Predictors of Weight Gain After Smoking Cessation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

ABSTRACT OF RESEARCH RESULTS

This study is (1) assessing the extent of weight gain in women over a one-year period after they quit smoking; (2) evaluating the role of diet, physical activity, and psychosocial factors as predictors of weight gain; and (3) examining the relationship between attitudes about weight gain and relapse after a cessation attempt. Over 500 women smokers, age 20 to 70, are being recruited for the study from smoking cessation classes of the Kaiser Permanente Medical Care Program in Northern California. Women who successfully quit are being followed for one year. Questionnaires and in-person measurements are done at baseline (prior to quitting), one month, six months, and one year. Dietary recalls are done by telephone twelve times over the year.

The three-year project is ending its first year. A half-year start-up phase included the development and pilot testing of research protocols and instruments, and training of 8 Research Assistants and Nutritionists. Recruitment began in mid February, 1991. By the end of June, 1991, we project that 170 women will have completed baseline data protocols including a questionnaire, bodily measurements, and dietary recalls. By that time, over 65 participants will have completed the one-month follow-up assessment. Projections based on the first three months of data collection indicate a need to increase the baseline sample size from 500 to about 620, since the numbers of enrolled women who never quit or who are early relapsers are larger than anticipated.

2023471080

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

La Jolla Cancer Research Foundation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
5 $1,272,215

b) The subject of research grants by academic discipline:
Cancer = 4
General Biomedical Science = 1

c) The relationship between State and Federal funding for tobacco research:
Other State = 0
Federal = $34,000

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
1 $75,600

g) The number and species of animals used in research:
Mice = 12/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
1 $75,600

Grant Recipient(s):

1. Cox, Adrienne Cancer
Ras prenylation, cholesterol biosynthesis and lung cancer
$75,600 (7/91-6/93)

2. Kohwi, Yoshinori Cancer
Studies in genotoxicity of tobacco-related carcinogens
$288,000 (7/90-6/93)

3. Pfahl, Magnus Cancer
Analysis of retinoid mediated anti-cancer activities
$757,415 (7/91-6/94)

4. Quilliam, Lawrence Cancer
Involvement of ras and krev-1 in lung cancer
$75,600 (7/91-6/93)

5. Zhang, Xiao-kun Gen Biomed
Molecular mechanism of retinoic acid action
$75,600 (7/90-6/92)

AWARD # CT98 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Yoshinori Kohwi, Ph.D.

INSTITUTION La Jolla Cancer Research Foundation

TITLE OF PROJECT Studies in Genotoxicity of Tobacco-related Carcinogens

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to study, at a sequence level, whether DNA topology affects the specificity of tobacco-related chemical carcinogen reactions with DNA. To understand the mechanism by which chemical carcinogens cause cancer, it is important to know which sites of chromatin are the critical targets for carcinogen modifications and the consequence of these reactions. During the first fiscal year I employed chloroacetaldehyde (CAA), a reactive metabolite of the carcinogen, vinyl chloride, as a probe to determine if non-B DNA structures exist *in vivo*. I successfully established the assay condition that can detect one such non-B DNA structure, a dG.dG.dC. triplex formation in *E. coli* cells (manuscript in preparation). This method can be used to screen tobacco-related chemical carcinogens for their interactions with DNA *in vivo*. I have also examined the mutation events of poly(dG)-poly(dC) sequences in *E. coli* cells and found that the deletion mutation depends critically on the poly(dG)-poly(dC) length. This length dependency reflects the potential of the poly(dG)-poly(dC) sequence to adopt a dG.dG.dC. triplex structure. Thus, it was strongly suggested that the deletion mutation is mediated by the formation of the triplex structure *in vivo* (manuscript in preparation). This mutation analysis serves as the basis for further studies on how chemical carcinogens induce mutations.

AWARD # FT 30 AWARD PERIOD 1990-1992

PRINCIPAL INVESTIGATOR Xiao-kun Zhang

INSTITUTION La Jolla Cancer Research Foundation, La Jolla

TITLE OF PROJECT Molecular Mechanism of Retinoic Acid Action

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Vitamin A and other retinoids are potent inhibitors of cancers. The mechanism underlying the cancer preventive effects of these compounds is still poorly understood. The aim of this project is to elucidate the molecular mechanism by which retinoic acid receptors (RARs) mediate the profound effect of retinoids, and in particular characterize the proteins which interact with and regulate the activities of RAR.

Interaction between RAR and c-Jun/cFos, the components of AP-1, was discovered by us. In the presence of RA, RAR inhibits the transcriptional activity of cJun/cFos while cJun/cFos can antagonize the RAR activity. This inhibition is due to an interaction between RAR and AP-1 that results in mutual loss of DNA binding activity. Thus, RAR in the presence of retinoids can directly interfere with the signal transduction pathway used by many growth factors and viral and cellular oncogenes. This finding allows an explanation at the molecular level of the potent anti-neoplastic effects observed for many retinoids.

Thyroid hormone receptors (TRs), in the absence of T3, have been shown to inhibit RAR activity on certain responsive elements by a mechanism that involves competitive DNA binding. Analysis of RAR and TR hybrid receptors revealed that their DNA binding activity is controled by their ligand binding domain (LBD). Hybrid receptors with LBD from RAR behaved like RAR. Thus, the LBD of a nuclear receptor largely influences the receptors DNA binding activity and therefore determines their positive and negative transcriptional activity.

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Grant Awards by Institution

2023471081

Source: https://www.industrydocuments.ucsf.edu/docs/wmgb0000

Lawrence Berkeley Laboratory

Grant Awards by Institution

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

5 $1,744,113

b) The subject of research grants by academic discipline:

Cancer	= 1
Cardiovascular Disease	= 1
General Biomedical Science	= 2
Pulmonary Disease	= 1

c) The relationship between State and Federal funding for tobacco research:

Other State	= 0
Federal	= $165,000

d) The relationship between each project and the overall strategy of the research program:

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

1 $417,585

g) The number and species of animals used in research:

Rats = 36/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

1 $417,585

Grant Recipient(s):

1. Bastacky, Jacob Pulmonary
Effects of tobacco on rat lung alveolar lining liquid
$417,585 (7/90-6/93)

2. Daisey, Joan Gen Biomed
Characterization of particulate-phase ets in differing envir.
$455,309 (7/90-6/93)

3. Forte, Trudy Cardiovascular
Effect of cigarette smoke on high risk lipoprotein profiles
$333,018 (7/91-6/94)

4. Mehlhorn, Rolf Joachim Gen Biomed
Hemoglobin conversion to pro-oxidants by cigarette smoke
$313,201 (7/90-6/93)

5. Tischler, Allan N. Cancer
Tobacco-related carcinogens in human epithelial cells
$225,000 (7/90-6/93)

AWARD # 1RT 448 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Jacob Bastacky

INSTITUTION Lawrence Berkeley Laboratory, University of California

TITLE OF PROJECT *Effects of Tobacco on the Rat Lung Alveolar Lining Liquid*

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to determine the effects of tobacco smoke on the amount of liquid in the air sacs or alveoli in the gas exchange portion of the lung. Such liquid is present as the alveolar lining layer at the surface of the wall of the alveolus, as blood in the capillaries in the alveolar wall, and as interstitial fluid in the connective tissue of the alveolar wall. All of these liquids are important in the normal functioning of the lung as well as the pathophysiology of common, serious diseases and in the response of the lung to environmental changes in inhaled air. Our low-temperature scanning electron microscope allows us to preserve such liquid as ice in frozen hydrated lung samples prepared under carefully controlled physiologial conditions.

During the first months of this project we have:

1) Obtained and tested a Walton smoking machine;
2) Designed a second smoking machine that delivers a controlled, high dose of cigarette smoke to the lungs of anaesthetized rats;
3) Built and tested several versions of the newly designed smoking machine;
4) Exposed rats to a single high dose of cigarette smoke for approximately 15 minutes;
5) Assessed acute structural changes in pulmonary alveoli exposed to this cigarette smoke with the following scanning electron microscope procedures:
   a) freezing the lungs *in vivo* under controlled physiological conditions;
   b) cutting small portions of the frozen lung and transferring them to the low-temperature scanning electron microscope;
   c) examining and photographing alveoli in the frozen hydrated state in the low-temperature scanning electron microscope at magnifications up to 10,000 X.

Preliminary results with the first 3 of 4 animals studied indicate that there were changes in alveoli of rats immediately after acute exposure to high doses of cigarette smoke. These changes appeared both in the alveolar lining layer and in the microvasculature of the alveolar wall. We are currently defining these changes and developing theoretical models for the smoke-induced ultrastructural changes.

AWARD # 1RT0299 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Joan M. Daisey

INSTITUTION University of California, Berkeley - Lawrence Berkeley Laboratory

TITLE OF PROJECT Characterization of Particulate-Phase ETS in Differing Environments

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Environmental tobacco smoke (ETS) is one of the common pollutants encountered in indoor spaces and it is estimated to cause up to several thousand cases of lung cancer per year as well as other adverse health effects. However, most studies of the health risks due to ETS have been based on estimates of exposure rather than actual lung dose. Many of the known carcinogens created in tobacco combustion reside in the particle (tar) phase of ETS and particle size is one of the key parameters affecting lung deposition of particles.

We are investigating the factors affecting the size distribution and concentration of ETS particles in order to provide a more accurate means of estimating the lung dose of these pollutants. Among these factors will be smoke generation rate, ventilation and air circulation, indoor temperature and relative humidity, aerosol aging, and room or enclosure size. The study will consist of both modeling and experimental components, and the experiments will combine both laboratory and field measurements. Sites for the field portion of the work will be selected to represent the major types of exposure setting (*e.g.* residential and office locations). This work will also examine the effect of air cleaning on particle sizes and concentrations under actual field conditions.

The experimental data will be used to further validate and extend an existing model of indoor aerosol dynamics. The model will then be used to examine parametrically the effects of different exposure conditions on ETS particle size and behavior indoors. In this way, the results of this project can be extended to estimate the dose of ETS particles in different exposure settings.

Progress has been made on two major aspects of this research. We have used our model of indoor aerosol dynamics and data from a set of previous experiments to determine the average emission profile for smoke from cigarettes. We have also begun the task of setting up and testing our instrumentation and computer-based data acquisition system in preparation for our experiments in our indoor air research facility.

2023471082

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

AWARD # 1 RT 88 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Rolf J. Mehlhorn

INSTITUTION University of California, Berkeley - Lawrence Berkeley Laboratory

TITLE OF PROJECT Hemoglobin Conversion to Pro-Oxidants by Cigarette Smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project seeks to characterise the degradation of hemoglobin by tobacco smoke components, which is postulated to release iron, lead to a suppression of cellular antioxidant defenses and generate organic products that can damage red blood cells and propagate damage to other tissues, including the vasculature. In a paper published this year we have reported that organic peroxides, such as are known to be present in cigarette smoke, enter red blood cells and compromise the metabolic processes that maintain a pool of intracellular vitamin C. Glutathione, another major antioxidant that is found in all tissues, is depleted in peroxide-exposed red blood cells and this depletion is especially severe in people with G6PD deficiency, which is common in populations from tropical and sub-tropical regions of the world. In work not yet published, novel and sensitive assays have been developed for the detection of hemoglobin oxidation and iron release associated with this oxidation. Application of these techniques to peroxide-treated hemoglobin has yielded surprising new information, including a remarkable series of transformations of the hemoglobin molecule as it undergoes progressive oxidation. Surprisingly, our recent data indicate that powerful oxidants are released from peroxide-treated hemoglobin prior to iron release and that extensive oxygen consumption occurs in the absence of exogenous reductants. Such oxygen consumption may be an especially important damage mechanism of tobacco smoke in people with compromised lung function. Work in progress with cigarette smoke extracts indicates that the hemoglobin damage assays we have developed are highly sensitive to the oxidizing effects of these extracts.

AWARD # 1 KT 59 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Allan N. Tischler

INSTITUTION Lawrence Berkeley Laboratory

TITLE OF PROJECT Tobacco Related Carcinogens in Human Epithelial Cells

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

A program was initiated investigating the effect of individual cigarette smoke componentss on the activation of benzo[a]pyrene (B[a]P) in human mammary epithelial cells (HMEC). The goal of this study is to establish which components of cigarette smoke act as cocarcinogens, i.e. enhance the carcinogenesis of B[a]P, and which components do not. These results could shed light on the possible, but controversial role of cigarette smoke in human breast cancer. Considerable initial effort has gone into establishing a common protocol for conducting meaningful experiments. The basic protocol now in use involves pretreating HMEC cells with low concentrations of the potential cocarcinogens (0.1uM) for 16 hours followed by a 4 hour incubation with ^{3}H-B[a]P (0.4uM). The cells and media are then combined, extracted into an organic phase and analyzed by reverse-phase HPLC in order to determine the extent of activation of B[a]P as measured by the formation of the key intermediate, benzo[a]pyrene-7,8-dihydrodiol (B[a]P-diol), and 7-hydroxybenzo[a]pyrene (B[a]P-7-ol), a significant byproduct also derived directly from B[a]P. To date we have evaluated 6 different cigarette smoke components (benzo[e]pyrene, squalene, oleic acid, decane, NNK and catechol) under 2 different circumstances, i.e. cells in which the initial B[a]P oxidase is preinduced and cells in which it is not induced. Much greater enhancement of B[a]P activation is observed in experiments in which the initial oxidase is not induced, suggesting that a major mechanism for cigarette smoke cocarcinogenesis involves the activation of this critical oxidase. Under these conditions, most notable enhancement of B[a]P-activation is noted for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and catechol. Benzo[e]pyrene gave the unique result in that it significantly enhanced activation in uninduced cells and inhibited activation in induced cells. This result is consistent with the fact that benzo[e]pyrene is capable of inducing the critical oxidase and at the same time compete with B[a]P as a substrate for this same oxidase.

2023471083

Source: https://www.industrydocuments.ucsf.edu/docs/[illegible]

3

Grant Awards by Institution

Lawrence Livermore National Laboratory

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

1 $344,430

b) The subject of research grants by academic discipline:

Engineering = 1

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Biermann, Arthur Engineering

Radon attachment to cigarette smoke aerosols

$344,430 (7/91-6/94)

2023471084

Source: https://www.industrydocuments.ucsf.edu/docs/ltyl0000

Loma Linda University

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

2 $499,429

b) The subject of research grants by academic discipline:

Epidemiology = 1
Tobacco Use Prevention, Intervention, and Cessation = 1

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program:

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Abbey, David Epidemiology
Chronic respiratory effects of past and passive smoking
$121,461 (7/91-6/92)

2. Lee, Jerry W. Intervention
Impact of caffeine use on tobacco cessation & withdrawal
377,968 (7/90-6/92)

AWARD # RT 532 AWARD PERIOD July 1, 1990 - June 29, 1991

PRINCIPAL INVESTIGATOR Jerry W. Lee, Ph.D.

INSTITUTION Loma Linda University, Loma Linda, CA

TITLE OF PROJECT "Impact of Caffeine use on Tobacco Cessation and Withdrawal"

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

OBJECTIVES: 1) To determine if reduction or elimination of caffeine aids in smoking cessation. 2) To determine how caffeine consumption contributes to the tobacco withdrawal syndrome. 3) To determine whether the two tobacco withdrawal syndromes suggested by our previous research are both related to tobacco withdrawal or whether one is simply the result of simultaneous caffeine withdrawal. 4) To determine whether there is a relationship between personality, motivation for smoking, and withdrawal symptoms. 5) To determine whether early caffeine recidivism precedes and predicts tobacco recidivism.

The project is now in the data collection and data entry phase. As of June 27, we have 32 of 200 volunteer participants in the research. Several factors have resulted in delays in the project timetable, they include: changes in data collection site, from Fontana Kaiser Permanente to American Lung Association (A.L.A.) of the Inland Counties. The Kaiser physicians have taken a more rigid stand on prescribing nicorette gum and anti-depressant drugs to program participants use of which would interfere with assessment of withdrawal symptoms; delay in starting the project, because funding was not received until October, 1990 and ; small numbers of participants and cancellations at the A.L.A. "Freedom from Smoking" collection sites (we are currently looking for additional A.L.A. program sites in the Los Angeles and Orange Counties).

Despite these delays the project has progressed in several areas. Two instruments have been developed and processed with more than 200 volunteer smokers: (1) "Feeling Profile" - withdrawal symptoms of caffeine, caffeinism, and nicotine; and (2) " Why Do You smoke" questionnaire. Questionnaires used for baseline intake measurements and also a "daily-log" for recording daily consumption patterns of nicotine and caffeine and withdrawal symptoms were developed and processed. Other standardized questionnaires in use include; Eysenck Personality Test and the 10-item Trait Anger Scale of the State-Trait Anger Expression Inventory. Protocol for sputum collection, analysis and storage are in place. Student Research Assistants from Loma Linda University have been hired and are available on an hourly basis to aid in data collection.

Grant Awards by Institution

20234710B5

Source: https://www.industrydocumentslibrary.ucsf.edu/tobacco/tw0000

Grant Awards by Institution

Long Beach Research Foundation/ Veterans Administration Medical Center

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
1 $186,945

b) The subject of research grants by academic discipline:
Tobacco Use Prevention, Intervention, and Cessation = 1

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program:
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
0

g) The number and species of animals used in research:
N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
N/A

Grant Recipient(s):

1. Berry, Richard Intervention
The role of sleep in successful smoking cessation
$186,945 (7/90-6/92)

AWARD # RT 546 AWARD PERIOD 1990-1991 Ans'd.....

PRINCIPAL INVESTIGATOR Michael H. Bonnet, Ph.D.

INSTITUTION Long Beach VA Medical Center

TITLE OF PROJECT The role of sleep in successful smoking cessation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Difficulty sleeping at night combined with daytime fatigue is one of the most commonly reported symptoms of individuals who stop smoking. This study examined the effect of smoking cessation on sleep quality, daytime sleepiness, and mood. Twelve subjects (8 men, 4 women) aged 35-49 years who had smoked at least 20 cigarettes per day for over 2 years were studied. Subjects were studied on three consecutive weeks (week 1 - nights 1,2,3; week 2 - nights 4,5,6; week 3 - nights 7,8). Sleep studies on each night included monitoring of brain waves, eye movements, and chin muscle tone to detect the presence and stage of sleep. To determine the degree of daytime sleepiness, five nap studies spaced throughout the following days measured how rapidly the subjects fell asleep (sleep latency). Daytime testing included testing of mood and anxiety as well as rating of symptoms commonly associated with smoking withdrawal. Subjects discontinued smoking three hours before bedtime on night 4. They had the option to either continue smoking cessation or to resume smoking during the third week. Data collected when the subjects smoked was compared with that during non-smoking days and nights.

Analysis of the nap data showed a decrease in sleep latency during smoking cessation. This indicates an increase in daytime sleepiness. Although no significant differences in total sleep time or the fraction of time subjects spent in each sleep stage were noted in the smoking and non-smoking conditions, there was an increase in the number of sleep stage changes during smoking cessation. This is an indicator of sleep disturbance. During smoking cessation, subjects were more anxious, had less vigor, were more irritable, and had increased cigarette craving. We conclude that smoking cessation is associated with an increase in daytime sleepiness which is due to an impairment in sleep quality as well as withdrawal from a stimulant (nicotine).

2023471086

Source: https://www.industrydocuments.ucsf.edu/docs/...

March of Dimes Birth Defects Foundation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
2 $1,287,994

b) The subject of research grants by academic discipline:
Epidemiology = 2

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
0

g) The number and species of animals used in research:
N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
N/A

Grant Recipient(s):

1. Shaw, Gary M. Epidemiology
Risks for selected birth defects from parental cigarette smoke
$554,085 (7/90-6/93)

2. Torfs, Claudine Epidemiology
Smoking as a risk factor in the etiology of Down syndrome
$733,909 (7/91-6/94)

AWARD # RT 466 AWARD PERIOD 7/90 - 6/93 mo's

PRINCIPAL INVESTIGATOR Gary M. Shaw, DrPH

INSTITUTION March of Dimes Birth Defects Foundation

TITLE OF PROJECT Risks For Selected Birth Defects From Parental Cigarette Smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Congenital malformations are the leading cause of infant mortality in the United States, however, for an estimated 70 percent of congenital malformations the determinants are unknown. Although a few suggestive observations have been made, little attention has been given to the potential associations between parental cigarette smoking or passive exposure to smoke during pregnancy and various congenital malformations in offspring. The objective of our epidemiologic investigation is to determine whether a relation exists between parental exposure to cigarette smoke and the selected congenital malformation groupings: oral clefts, neural tube defects, conal-truncal defects, and limb reduction defects. The study is currently in its start-up phase with the expectation that nearly 2,000 women who have had a child with or without a birth defect will be interviewed over the next year about their pregnancies. Many problems associated with earlier work will be circumvented by employing a well-designed epidemiologic study using population-based data and soliciting detailed exposure information via maternal interviews. Results of our investigation are anticipated in early 1993.

2023471087

Source: https://www.industrydocuments.ucsf.edu/docs/[illegible]

3

Grant Awards by Institution

Northern California Institute for Research and Education

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

3 $501,199

b) The subject of research grants by academic discipline:

Cardiovascular Disease = 1
Public Health, Public Policy, and Economics = 1
Tobacco Use Prevention, Intervention, and Cessation = 1

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

1 $75,600

g) The number and species of animals used in research:

Rats = 100/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

1 $75,600

Grant Recipient(s):

1. Carmody, Timothy Intervention
Affect regulation in the prevention of smoking relapse
$85,583 (7/91-6/92)

2. Halliday, Roy Pub Health
Effects of nicotine on human information processing
$340,016 (7/90-6/92)

3. Kwasman, Michael Pulmonary
Direct effect of nicotine on the early outward K channel
$75,600 (7/91-6/93)

AWARD # 1 RT 144 AWARD PERIOD 7/1/90-6/30/92

PRINCIPAL INVESTIGATOR Roy Halliday, Ph.D. UCSF

INSTITUTION Northern California Institute of Research and Education (NCIRE)

TITLE OF PROJECT Effects of Nicotine on Human Information Processing

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Although there are many reasons why people begin and continue to smoke, one reason smokers commonly report is that smoking improves their concentration and ability to think clearly. There are objective correlates of these self reports. Many studies have shown that smoking improves performance on standardized information processing tasks in smokers. There is also evidence that this performance improvement is due to the effects that nicotine (NIC) has on neurotransmitter activity --the biochemical processes that mediate the communication between nerve cells. The specific neurotransmitter (NT) systems responsible for the performance effects are not known. The purpose of this project is 1) to determine the specific cognitive processes that are changed by nicotine, 2) to relate the cognitive effects to specific NT substrates, and 3) to relate the NIC effects to a comprehensive theory of cognitive-neuropharmacology so that we can better understand the properties of drugs that are abused. To achieve these goals we record behavioral and electrophysiological responses while subjects perform a standardized task. Measures derived from these responses allow us to identify where in the temporal flow of information processing particular drugs act. For example, cholinergic and noradrenergic drugs act early in processing, while adrenergic drugs act late. The information processing measures together with pharmacological agents that decrease or increase the effects of nicotine should provide important data on the cognitive effects of nicotine and help to the search for therapeutic methods to improve smoking cessation.

2023471088

Source: https://www.industrydocuments.ucsf.edu/docs/ltvd0000

Palo Alto Medical Research Foundation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
1 $325,994

b) The subject of research grants by academic discipline:
General Biomedical Science = 1

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
1 $325,994

g) The number and species of animals used in research:
Mice = 1200/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
0

Grant Recipient(s):

1. Fong, Loren Gen Biomed
Cytokines and foam cell formation
$325,994 (7/90-6/93)

3

Grant Awards by Institution

WARD # KT145 AWARD PERIOD 7/90-6/91

RINCIPAL INVESTIGATOR Loren Gi Fong, Ph.D.

NSTITUTION Palo Alto Medical Research Institute

ITLE OF PROJECT Cytokines and Foam Cell Formation

lease summarize, in language understandable by an educated layman, the objective f this project and the significant findings resulting from the work. Limit the bstract to a space 6" by 8.5".

Atherosclerosis is a slow progressive disease that is characterized by a buildup of excessive amounts of cholesterol in the artery. Studies of the developing atherosclerotic lesion in animal models have demonstrated that the cholesterol deposits are actually located inside a particular cell type called the macrophage and that the cholesterol originates from lipoproteins that circulate in the bloodstream. Subsequent studies that focused on macrophage lipoprotein metabolism identified a receptor on their cell surface termed the scavenger receptor which recognizes and processes modified forms of lipoproteins that can lead to cholesterol deposition. The overall objective of this research proposal is to study the regulation of the macrophage scavenger receptor pathway. Based on preliminary findings from our laboratory, we have formulated a working hypothesis of how the macrophage scavenger receptor is regulated in the artery wall by factors called cytokines; cytokines produced by artery wall cells including macrophages modulate the activity of the scavenger receptor and thus the rate of cholesterol deposition and the production of cytokines are inturn controlled by lipoproteins. Together this feedback mechanism provides the means for the regulation of cholesterol deposition. During the past year, our studies have focused on the regulation of cytokine production by lipoproteins. These studies have been fruitful and a manuscript describing this work has been submitted to the Journal of Lipid Research for publication. Briefly, we have determined that one type of modified lipoprotein called oxidized LDL inhibits the synthesis of cytokines by macrophages. The inhibitory activity has been characterized and the active component identified as a lipid. The identification of the active lipid species is currently ongoing and hopefully may lead to the design of new drugs to modulate cytokine production.

2023471089

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

3

Grant Awards by Institution

Public Health Foundation of Los Angeles

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

1 $524,044

b) The subject of research grants by academic discipline:

Engineering = 1

c) The relationship between State and Federal funding for tobacco research:

Other State = $16,000
Federal = 0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Hayward, Steven B. Engineering
Effectiveness ventilation & other controls in reducing ets
$524,044 (7/90-6/93)

AWARD # RT 505 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Steven B. Hayward

INSTITUTION The Public Health Foundation of Los Angeles County, Inc.

TITLE OF PROJECT Effectiveness of Ventilation & Other Controls in Reducing ETS

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this research project was to evaluate the effectiveness of various control measures for protecting non-smokers in office buildings from environmental tobacco smoke (ETS) generated by smoking within the building. These measures were to include, but not be limited to, 1) providing non-smoking working and/or eating areas adjacent to smoking areas and served by the same ventilation system, 2) requiring smoking and non-smoking areas to be separated by walls, 3) providing exhaust-only ventilation for non-smoking areas, and 4) providing separate (recirculating) ventilation systems for smoking areas.

The study was designed to be carried out in approximately 30 buildings in California, in which smoking is allowed only in smoking areas. In each building, smoking patterns were to be logged. Several components of ETS (nicotine, particles, and tarry particles) were to be measured in one smoking area and in two or three non-smoking areas. Tracer gas measurements were also to be used to determine the movement of air from smoking to non-smoking areas, and to correlate these results with the ETS measurements.

Because notice of award was not received until July, 1990, and advertising to fill the two positions funded by the grant did not begin until that time, only one qualified applicant had been located by October, 1990. He was not able to start work until January, 1991. The effective term for this report is therefore only six months. During that time, equipment to sample for nicotine and particles was purchased, assembled, and tested. Equipment to measure air flows and ventilation rates using a tracer gas was purchased and tested, and laboratory equipment to analyze air samples for nicotine and particles was set up and tested. Finally, a random selection of cities and counties based on population was carried out, resulting in the selection of 72 cities and 30 counties. These cities and counties will be contacted to arrange for office buildings to be included in the study. Finally, personnel responsible both for buildings and smoking policy within these jurisdictions have been identified through a telephone survey.

2023471090

Source: https://www.industrydocuments.ucsf.edu/docs/rvl0000

The Rand Corporation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

2 $407,225

b) The subject of research grants by academic discipline:

Public Health, Public Policy, and Economics = 2

c) The relationship between State and Federal funding for tobacco research:

Other State = 20,000
Federal = 0

d) The relationship between each project and the overall strategy of the research program:

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. Jacobson, Peter Pub Health
Case study on tobacco use legislation
$161,907 (7/90-6/92)

2. Valdez, Robert Pub Health
The cost of passive smoking on children's health
$245,318 (7/91-6/93)

PRINCIPAL INVESTIGATOR Peter D. Jacobson

CAMPUS/INSTITUTION RAND

AWARD # 1RT529 AWARD PERIOD 7/1/90-6/30/91

TITLE OF PROJECT Case Study on Tobacco Use Legislation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 7".

One of the most promising approaches in efforts to limit cigarette smoking, and one that has been used with increasing frequency at all levels of government over the past 10 to 15 years, is legislation that restricts or prohibits smoking in public places. To date, however, there has been no attempt to identify and study the determinants across states that explain the outcomes of proposed tobacco control legislation. Using a case study methodology, this project explains and evaluates the process by which tobacco control initiatives become law.

We examined the political evolution of tobacco control initiatives in six states: Florida, Illinois, Minnesota, New York, Texas, and Arizona. Data were derived primarily from interviews with public officials and with representatives from groups and organizations on both sides of the issue. Through these case studies, we examined the influence of a number of explanatory factors on legislative outcomes, including the public health environment, political leadership, the strategies pursued by tobacco control advocates and the tobacco lobby, and the state's demographic profile.

We conclude that the key factors leading to the enactment of tobacco control legislation are the existence of an organized anti-smoking coalition and the ability of key legislators to support or block legislation. Each is a necessary, but not sufficient, determinant of the legislative process. The formation of an anti-smoking coalition and the concomitant hiring of sophisticated lobbyists are needed to translate effectively public sentiment against smoking into legislation.

How the issue is framed is also an important component of the legislative outcome. When anti-smoking organizations are able to frame the issue as one of public health, there is a higher probability of enacting anti-smoking legislation than when the tobacco industry is able to frame the issue as one of personal freedoms. Recent evidence of the harm from second hand smoke, however, appears to have blunted the personal freedoms argument in several states.

We also conclude that tobacco legislation follows a separate legislative track from other public health legislation, and that state medical society involvement is important, though usually peripheral, in legitimating the public health arguments.

The study's findings will be useful to state legislators and other public health officials involved in formulating tobacco control legislation. These findings will also provide insight into how other public health initiatives might effectively be presented to state legislatures.

3

Grant Awards by Institution

2023471091

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

3

Grant Awards by Institution

Research and Education Institute/ UCLA-Harbor Medical Center

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
4 $909,963

b) The subject of research grants by academic discipline:
Cardiovascular Disease = 1
General Biomedical Science = 1
Pulmonary Disease = 2

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
1 $75,600

g) The number and species of animals used in research:
Rabbits = 40/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
0

Grant Recipient(s):

1. Daly, James Pulmonary
Smoking & COPD: effects on cerebral perfusion & function
$300,000 (7/90-6/93)

2. Jensen, Steven Cardiovascular
Regulation of CO2 transport in circulatory & respiratory failure
$75,600 (7/91-6/93)

3. Poland, Russell Gen Biomed
CNS effects of prenatal nicotine exposure: threshold dosage
$458,763 (7/91-6/94)

4. Rosenberg, Scott Pulmonary
effects of cigarettes and carbon monoxide on exercise in cop
$75,600 (7/90-6/92)

AWARD # ET84 AWARD PERIOD 7/01/90-6/30/91

PRINCIPAL INVESTIGATOR James A. Daly, M.D.

INSTITUTION Research and Education Institute, Inc. Harbor-UCLA Medical Center

TITLE OF PROJECT Smoking and COPD: Effects on Cerebral Perfusion and Function

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cigarette smoking is an important factor in the development of cerebrovascular disease and chronic obstructive pulmonary disease (COPD). These disorders are commonly associated with abnormalities of brain function. We hypothesize that changes in blood flow to the brain (unrelated to atherosclerotic vascular disease) may be an important mechanism underlying neurologic disturbances and possibly increasing the risk of stroke. The objective of this project is to study the effect of: 1) cigarette smoking and smoking cessation on brain blood flow and 2) COPD with low blood oxygen level on brain function, metabolism, and blood flow. Data from study participants are too limited at this time to draw firm conclusions.

AWARD # PT-59 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Scott B. Rosenberg M.D.

INSTITUTION Research and Education Institute, Inc. Harbor-UCLA Medical Center

TITLE OF PROJECT Effects of Cigarettes and Carbon Monoxide on Exercise in COPD Patients

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The vast majority of patients with emphysema have some degree of exercise limitation. Their respiratory system may limit exercise(by abnormal lung mechanics) or they may have cardiovascular limitation to exercise(by cardiac dysfunction, pulmonary vascular disease, or coronary artery disease). Cigarette smoking is a primary cause of emphysema and cardiovascular disease; therefore many patients have coexistent disease. Cigarette smoking and its resultant carbon monoxide production have previously been shown to exacerbate cardiac dysfunction in subjects with known cardiovascular disease,however, its effects in patients with emphysema are uncertain. The objective of this study is to determine the acute effects of cigarette smoking on exercise capacity, and the potential causes of these effects.

At this point in the study 8 currently smoking patients with emphysema who had no demonstrable cardiac disease have been recruited. We performed exercise tests that measure heart and lung function on each of these patients under 3 separate conditions: (1) after abstaining from smoking and breathing oxygen to eliminate residual carbon monoxide in their blood, (2) after smoking 3 - 4 cigarettes per hour for 2 hours, and (3) after abstaining from smoking and then breathing a small concentration of carbon monoxide in order to obtain a blood level similar to that measured while smoking.

Results on these 8 patients show a decline in cardiovascular function during exercise in the smoking inhalation phase of the study when compared to the non-smoking and carbon monoxide inhalation phases of the study. Although there was little change noted in the subjects' pulmonary function during the study, the amount of breathing required was higher at similar levels of exercise in the tobacco smoking phase. These findings suggest that smoking causes a reduction in exercise capacity in patients with emphysema by adversely affecting their cardiovascular function and thereby increasing the demand on their already stressed respiratory system. These effects appear to be due to substances, such as nicotine, inhaled while smoking.The effects of carbon monoxide are still uncertain.

2023471092

Source: https://www.industrydocuments.ucsf.edu/docs/fvy00000

The Salk Institute for Biology

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
3 $1,208,002

b) The subject of research grants by academic discipline:
General Biomedical Science = 3

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
2 $1,132,402

g) The number and species of animals used in research:

Frogs	= 50/year
Mice	=500/year
Rabbits	= 2/year
Rats	=100/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
0

Grant Recipient(s):

1. Heinemann, Stephen Gen Biomed
Regulation of the nicotinic receptors by nicotine
$756,102 (7/90-6/93)

2. Hoekstra, Merl Gen Biomed
Molecular analysis of a DNA repair function
$376,300 (7/91-6/94)

3. Wisdom, Ronald Gen Biomed
Regulation of transformation by the fos gene
$75,600 (7/91-6/93)

AWARD # 1RT-366 AWARD PERIOD 07/01/90 - 06/30/93

PRINCIPAL INVESTIGATOR Stephen F. Heinemann

INSTITUTION The Salk Institute for Biological Studies

TITLE OF PROJECT Regulation of the Nicotinic Receptor by Nicotine

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The epidemic of tobacco use in industrialized societies is driven by the desire to feel the effects of nicotine. Unfortunately, the most convenient way to deliver nicotine to the body, rapidly and at high doses, is by smoking cigarettes. Nicotine is one of the most widely taken addictive drugs and the history of the cultivation of tobacco suggests that early man appreciated the behavioral effects of nicotine. About one third of the adult population of the United States is addicted to nicotine which has led to an epidemic of lung cancer and heart disease in the United States and many of the industrialized countries. The less developed countries of the world increasingly face a similar fate. As is the case for chemical addiction in general, the mechanism of nicotine addiction is not known. During the past few years we have discovered a large family of nicotinic receptors expressed in the brain. The primary goal of this proposal is to understand the physiological functions of these brain nicotinic receptors that until a few years ago remained unknown. This work will include the characterization of new nicotinic receptors using a combination of gene cloning and physiological techniques. The effects of nicotine on the expression of the nicotinic receptor genes will be studied during the development of the embryo and in adult mouse brains. If nicotine is found to effect the expression of the nicotinic receptor genes during the development of brain this will have profound implications for human health. The effect of smoking on the expression of the nicotinic receptor genes in the adult human brain will also be studied. Finally, cell lines expressing specific cloned brain nicotinic receptors will be made as a step toward the development of screening systems for drugs that could be used to treat nicotine addiction.

3

Grant Awards by Institution

2023471093

Source: https://www.industrydocuments.ucsf.edu/docs/ltyl0000

3

Grant Awards by Institution

San Diego State University Foundation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

6 $5,077,829

b) The subject of research grants by academic discipline:

Cardiovascular Disease = 1
Public Health, Public Policy, and Economics = 1
Tobacco-Use Prevention, Intervention, and Cessation = 4

c) The relationship between State and Federal funding for tobacco research:

Other State = $170,000
Federal = $135,000

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

1 $447,480

g) The number and species of animals used in research:

Rats = 350/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

1 $447,480

Grant Recipient(s):

1. Elder, John P. Intervention
Experimental approach to tobacco control for high-risk teens
$654,152 (7/90-6/93)

2. Glembotski, Christopher Cardiovascular
Mechanism of endothelin-stimulated anf secretion
$447,480 (7/90-6/93)

3. Hovell, Melbourne Intervention
Reduction of passive smoking in asthmatic children:clinical trial
$522,773 (7/90-6/93)

4. Hovell, Melbourne Intervention
Clinician initiated smoking prevention: a controlled trial
$2,042,630 (7/91-6/94)

5. Martin, John Intervention
Smoking cessation in recovering alcoholic person (SCRAP)
$819,944 (7/91-6/94)

6. Sallis, James Pub Health
Assessing tobacco refusal skills in Latino youth
$590,850 (7/90-6/93)

2023471094

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

AWARD # 1RT519 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR John P. Elder, Ph.D., M.P.H.

INSTITUTION San Diego State University Foundation

TITLE OF PROJECT Experimental Approach to Tobacco Control for High Risk Teens

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The project's main research objective is an investigation of the effectiveness of an intensive peer facilitated smoking cessation and prevention program. The project will also assess the predictors of participation and success in this smoking control program through a detailed inspection of sociodemographic, social-psychological, familial, and academic variables. The contributing effects of an environmental and educational tobacco program among at-risk and not-at-risk continuation high school students will also be assessed.

A pilot of the questionnaire to be used for January, 1992 baseline was completed. Dependent measures included indices of current smoking and smokeless tobacco use, knowledge and attitudes toward tobacco, measures of "stages of change" toward the onset or cessation of tobacco use. A "bogus pipeline" saliva sample for cotinine analysis was taken for validation of the self-report.

A total of 83 students participated in the survey. This represents 12.5% of the student population at the participating continuation high schools. Findings indicate 54% of the students are at least weekly cigarette smokers. Smokeless tobacco is used weekly by 2% of the population. Respondents indicated that 32.5% have parents that smoke and 91% indicated having at least one close friend that smokes.

The intervention and cessation curriculum has been developed and will be pilot tested in July, 1991. The pilot consists of 8 lesson plans implemented by trained Peer Health Facilitators selected from the school's classroom population. The lessons provide in-depth coverage of tobacco issues in health, advertising influence, physiological impact, self-image, refusal skills, coping and communication skills during cessation, and relapse prevention.

AWARD # RT 317 AWARD PERIOD 7-01-91 to 6-30-92

PRINCIPAL INVESTIGATOR Christopher C. Glembotski

INSTITUTION San Diego State University

TITLE OF PROJECT Mechanism of Endothelin-stimulated ANF Secretion

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Endothelin (ET) is a potent vasoconstrictor peptide synthesized and released by vascular endothelial cells. We have found that ET is also a potent stimulator of the release of atrial natriuretic factor (ANF), a potent vasodilatory peptide, from the heart. The objective of the proposed study is to investigate the mechanism through which ET stimulates the secretion of ANF from primary atrial myocytes. The significant findings resulting from work carried out during the first year of funding are:

1. ET stimulates membrane phosphoinositide (PI) hyrolysis in atrial myocytes. This PI hydrolysis appears to correlate to some degree with the ability of ET to stimulate ANF secretion. This implies that protein kinase C (PKC) activation is critical to the mechanism of action of ET as a secretagogue.
2. ET stimulates PKC activity, as measured by the phosphorylation of MARKS, a ubiquitous cellular substrate for PKC, and to some extent this stimulation correlates with the ability of ET to stimulate ANF release. The time course of ET-stimulated PKC activation is such that maximal activation (about 1.5-fold over background) occurs within 2 min of ET application. Interestingly, this activation level remains relatively constant throughout the next 30 min, as long as ET is in the bathing medium.
3. Phorbol esters (e.g. TPA) stimulate PKC activation two- to three-fold better than does ET, however, TPA is a very poor stimulator of ANF secretion. These results suggest that the efficacy of ET as an ANF secretagogue may not be due fully to its ability to stimulate PKC activity. Perhaps ET stimulates secretion through other, PKC-independent pathways.
4. In testing the possible involvement of other protein kinases in the mode of action of ET, we found that KN-62, a specific and potent inhibitor of calcium/calmodulin kinase II (CaM K II) produced a partial inhibition of ET-stimulated ANF release. Thus, it is probable that both PKC activation and CaM K II activation are integral parts of ET-stimulated ANF release.

AWARD # TRT 509 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Melbourne Hovell

INSTITUTION San Diego State University Foundation

TITLE OF PROJECT Reduction of passive smoking in asthmatic children: a clinical trial

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The project objective is to reduce passive smoke exposure to children at risk from both upper and lower respiratory disease. The specific aims have been refined and modified as follows:

1. examine the effectiveness of a behavioral program in reducing home exposure levels in allergic and asthmatic children.
2. compare the effectiveness of counseling, self-monitoring and lowered tobacco exposure on respiratory symptoms.
3. validate self-reported smoking behaviors with use of home diffusion filter used as a room monitor along with collection of discarded cigarette butts.
4. examine the degree parents reduce or quit smoking as a result of participation in this project.

Our year one report is based on a seven-month actual schedule (see attached). The project is going well according to the adjusted timetable. Progress has been made in year one ensuring project objectives will be met. Most of year one has been spent in writing and testing behavioral measures including family history, self-monitoring instruments, as well as revisions of diffusion monitor protocol. A counseling tool was written to insure consistency among research staff in implementing intervention. Rapport with allergy clinic personnel has been established to give support to families and improve performance and retention. To date 25 families have been recruited including 12 families who have completed their first clinic visit.

AWARD # RT 588 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR James F. Sallis, PhD

INSTITUTION Department of Psychology, San Diego State University

TITLE OF PROJECT Assessing Tobacco Refusal Skills in Latino Youth

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Latino youth have a higher prevalence of tobacco use than do other ethnic groups in Southern California, and the even higher rates of use among youth in Tijuana, Mexico suggest that this cultural group is at high risk for tobacco related diseases. Because of suspected cultural factors in the acquisition of tobacco use, it is important to study tobacco use and its influences in Latino youth in California, as well as youth in Mexico, because many will immigrate to California. The purpose of the present study is to develop and evaluate a refusal skills test that is specifically developed for Latino youth that is linguistically and culturally adapted to this high-risk and rapidly growing population.

"Tobacco offer" situations that Latino youths in San Diego and Tijuana Mexico normally encounter were identified in focus groups. These situations will be used as the behavioral test of tobacco refusal skills. Four sets of these "tobacco offer" situations which include one set each for males and females in Spanish and English will be used with sixth and seventh grade students in Tijuana and San Diego.

Tobacco refusal skills materials for eight lesson plans were revised from existing tobacco prevention materials to meet the needs of Latino youths. A pilot intervention was conducted in two seventh grade classes in San Diego and one fifth grade class in Tijuana to test the materials. This intervention will be offered to 200 students in San Diego and 100 students in Tijuana during the coming fall and spring.

Over 800 youths in San Diego and Tijuana were surveyed to assess the incidence of parental encouragement to smoke in various ethnic groups. The "bogus pipeline" method was incorporated to increase validation of the self-report measure. These data are in the process of being analyzed.

2023471095

Source: https://www.industrydocumentslibrary.ucsf.edu/docs/ltvl0000

Scripps Clinic and Research Foundation

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

9 $3,314,558

b) The subject of research grants by academic discipline:

Cancer	= 2
Cardiovascular Disease	= 2
General Biomedical Science	= 4
Pulmonary Disease	= 1

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

7 $2,708,071

g) The number and species of animals used in research:

Mice	= 394/year
Monkeys	= 12/year
Rabbits	= 40/year
Rats	= 400/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

5 $1,557,345

Grant Recipient(s):

1. Bokoch, Gary Pulmonary
Regulation of oxidant production in activated phagocytes
$540,380 (7/91-6/94)

2. Elias, Darlene Cancer
Monoclonal antibody-drug conjugate treatment of lung cancer
$258,750 (7/90-6/93)

3. Griffin, John Gen Biomed
Interaction of complement C4b-binding protein with protein b
$616,016 (7/90-6/93)

4. Gruber, Andras Cardiovascular
Activated protein C in smokers thrombosis
$347,737 (7/91-6/93)

5. Henriksen, Steven Jon Gen Biomed
The accumbens: a critical brain site for nicotine craving
$534,710 (7/90-6/93)

6. Jackson, Janis Gen Biomed
Factors required for k-ras 4b membrane association/activity
$600,414 (7/90-6/93)

7. Jackson, Janis Gen Biomed
Factors required for k-ras 4b membrane assoc & activity
$164,736 (7/90-6/93)

8. Levin, Eugene Cardiovascular
Effect of nicotine on fibrinolytic responsiveness in vivo
$125,316 (7/91-6/94)

9. Rideout, Darryl Cancer
Selective lung tumor inhibition with 4-ipomeanol analogs
$126,499 (7/91-6/92)

AWARD # RT339 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Darlene J. Elias, M.D.

INSTITUTION Scripps Clinic and Research Foundation

TITLE OF PROJECT Monoclonal antibody-drug conjugate treatment of lung cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The overall aim of this project is a multidisciplinary study at the chemical, immunological, pharmacological and clinical levels of the mechanisms involved in monoclonal antibody (MoAb)-directed targeting of chemotherapeutic drugs to a human carcinoma-associated antigen expressed on non-small cell lung carcinomas.

A phase 1/II clinical trial using MoAb KS1/4-methotrexate drug conjugate in patients with advanced non-small cell lung carcinoma has been completed. Toxicities associated with the MoAb-conjugate infusions as well as the maximal tolerated doses have been determined. One patient had a minimal regression of lung tumor.

The second part of our project is the development of a cisplatin (CP) immunoconjugate. Complexation studies of CP with aconitic acid have been successfully completed. Studies of the conjugation of these CP complexes with protein material have been carried out using human serum albumin as the first test protein. We have been successful in the preparation of a protein that contains the active moiety of CP. Further studies regarding the structure, stability and immunoreactivity of these conjugates are ongoing.

2023471096

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

AWARD # 1RT 183 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Steven Jon Henriksen

INSTITUTION The Scripps Research Institute

TITLE OF PROJECT The Accumbens: A Critical Brain Site for Nicotine Craving

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The social, medical and economic consequeaces of human nicotine addiction have always been extreme. The recent report issued by HHS Secretary Louis Sullivan has further defined these costs and has estimated the dollar amount to exceed $52 billion annually. Recent behavioral and clinical research suggests that habitual use of addictive drugs arises in part from their reinforcing properties, or their ability to cause 'craving'. The reinforcing properties of nicotine is thought to result from an interaction with central neurons, and probably with the stereospecific nicotinic receptors for the natural, endogenous transmitter acetylcholine. However, the cholinergic literature suggests that most CNS regions have abundant cells or fibers containing acetylcholine and receptors. Further investigation of the bases of nicotine addiction then involves determining whether there is a specific brain region that is largely responsible for the reinforcing properties of nicotine and if so, what are the cellular or molecular mechanisms involved. Current hypotheses suggest that several brain regions are involved in the self-administration of drugs of abuse, the most important being an area in the basal forebrain, the nucleus accumbens (NACC), and the dopamine (DA)-containing ventral tegmental area (VTA) (12). The evidence for the NACC as a key area is predicated on the evidence obtained from our own studies demonstrating that local injections of antagonists into the NACC prevents, for example, intravenous heroin self-administration in rats. More directly with respect to nicotine, recent investigations have indicated that 6-hydroxy-dopamine lesions of dopamine terminals in the accumbens are able to block the stimulant effects of nicotine in rats. Progress obtained in our first year of funding has centered on developing the capability of recording NACC spontaneous neuronal activity in anesthetized and unrestrained rats. In the unanesthetized rat, accumbens neurons have higher rates of spontaneous activity than in the anesthetized subjects and appear to have highest rates during exploration of novel environments, and during REM sleep. These preliminary studies have verified that excellent cellular recordings can be made from this important brain region and that studies of nicotine action on this area are now possible.

AWARD # RT 304 AWARD PERIOD July 1, 1990-June 30, 1991

PRINCIPAL INVESTIGATOR John M. Griffin, Ph.D.

INSTITUTION The Scripps Research Institute

TITLE OF PROJECT Interaction of complement C4b-Binding Protein with Protein S

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The goal of the proposed research is to increase our understanding of the regulation of the antithrombotic plasma protein, protein S (PS), by complement C4b-binding protein (C4BP), especially as this relates to the increased risk of vascular disease and thrombosis in smokers. Over half of all deaths in the United States are a result of vascular disease, and it has been estimated that smoking is a key contributing factor in up to 40% of these deaths. The level of C4BP in plasma is associated with levels of cholesterol in low density and very low density lipoprotein, known risk factors for vascular disease. C4BP is an acute phase protein, and several other acute phase proteins are elevated in smokers. C4BP reversibly associates with PS in blood and PS in this PS:C4BP complex is inactive as an anticoagulant agent. We seek to determine whether C4BP is elevated in male and female smokers and how this affects the regulation of PS and its anticoagulant functions, all of which are poorly understood. An increase in C4BP in smokers would likely lead to an increase in PS-C4BP complex levels and a decrease in free, anticoagulantly functional PS. This would be predicted to be a significant risk factor since in numerous reported cases of familial PS deficiency, low levels of free PS are associated with thrombotic disease. Moreover, recent reports suggest that decreased free PS is associated with arterial thrombotic risk. We are developing new and improved assays to measure free and complexed PS and C4BP and functional PS in plasma of smokers and nonsmokers. Our results during this past year have demonstrated that the current literature information is fundamentally wrong in that the appearance of "free" PS in plasma results from the fact that PS is in significant molar excess over C4BP. Current studies are also concerned with identifying which molecular domains and sequences of PS and C4BP are involved in their interactions. Our results during this first year identified the region of PS containing amino acids 420-434 as essential for these interactions; this knowledge will permit development of a new assay specific for free PS.

AWARD # 1RT 120 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Janis H. Jackson, M.D.

INSTITUTION Scripps Clinic and Research Foundation

TITLE OF PROJECT Factors Required for K-ras 4B Membrane Association/Activity

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The overall goal of the proposed research is to determine the structural and biochemical factors involved in converting cytosolic human K-ras 4B protein into membrane-bound protein. Oncogenic human K-ras 4B protein is frequently detected in lung cancers of cigarette smokers, and it is believed that K-ras 4B protein may play a crucial role in the pathogenesis of these cigarette smoke-associated malignancies. Since oncogenic K-ras 4B must become membrane associated in order to malignantly transform cells, elucidation of the factors which enable K-ras 4B protein to become membrane associated may improve our understanding of the mechanism of action of ras, and may ultimately allow us to develop rational therapeutic interventions that might inhibit oncogenic K-ras 4B protein membrane association and prevent it from contributing to human lung carcinogenesis. Accordingly, the specific aims of our proposed research are to: 1) determine the posttranslational modifications of K-ras 4B protein; 2) determine which posttranslational modifications are important for K-ras 4B protein membrane association and biological activity; 3) determine the sequence in which the posttranslational modifications of K-ras 4B protein occur; and 4) determine the role of the polybasic domain in K-ras 4B protein membrane association and biological activity.

The most significant finding that we have obtained to date is that the polylysine domain plays an important role in K-ras 4B protein membrane association, and this domain appears to be crucial for K-ras 4B transforming activity. Moreover, our results suggest that the polylysine domain contributes to membrane association and transforming activity as a result of its positive charge. In addition, we have demonstrated that K-ras 4B protein becomes farnesylated, methylated and truncated. Our preliminary conclusion is that both the polylysine domain and posttranslational modifications are required for K-ras 4B protein membrane association and transforming activity.

AWARD # 1RT 298 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Janis H. Jackson, M.D.

INSTITUTION Scripps Clinic and Research Foundation

TITLE OF PROJECT Factors Required for K-ras 4B Membrane Association/Activity

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The overall goal of the proposed research is to determine the structural and biochemical factors involved in converting cytosolic human K-ras 4B protein into membrane-bound protein. Oncogenic human K-ras 4B protein is frequently detected in lung cancers of cigarette smokers, and it is believed that K-ras 4B protein may play a crucial role in the pathogenesis of these cigarette smoke-associated malignancies. Since oncogenic K-ras 4B must become membrane associated in order to malignantly transform cells, elucidation of the factors which enable K-ras 4B protein to become membrane associated may improve our understanding of the mechanism of action of ras, and may ultimately allow us to develop rational therapeutic interventions that might inhibit oncogenic K-ras 4B protein membrane association and prevent it from contributing to human lung carcinogenesis. Accordingly, the specific aims of our proposed research are to: 1) determine the posttranslational modifications of K-ras 4B protein; 2) determine which posttranslational modifications are important for K-ras 4B protein membrane association and biological activity; 3) determine the sequence in which the posttranslational modifications of K-ras 4B protein occur; and 4) determine the role of the polybasic domain in K-ras 4B protein membrane association and biological activity.

The most significant finding that we have obtained to date is that the polylysine domain plays an important role in K-ras 4B protein membrane association, and this domain appears to be crucial for K-ras 4B transforming activity. Moreover, our results suggest that the polylysine domain contributes to membrane association and transforming activity as a result of its positive charge. In addition, we have demonstrated that K-ras 4B protein becomes farnesylated, methylated and truncated. Our preliminary conclusion is that both the polylysine domain and posttranslational modifications are required for K-ras 4B protein membrane association and transforming activity.

2023471097

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

SRI International

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

6 $2,548,352

b) The subject of research grants by academic discipline:

Cancer	= 1
Cardiovascular Disease	= 2
General Biomedical Science	= 2
Tobacco Use Prevention, Intervention, and Cessation	= 1

c) The relationship between State and Federal funding for tobacco research:

Other State	= 0
Federal	= $89,000

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

3 $1,417,927

g) The number and species of animals used in research:

Guinea Pigs	= 40/year
Rats	= 1,000/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

2 $706,185

Grant Recipient(s):

1. Hiebert, Charles — Gen Biomed
Novel benzoxazinone inhibitors to human leukocyte elastase
$345,758 (7/90-6/93)

2. Hiebert, Charles — Gen Biomed
Peptidyl phosphonate inhibitors to human leukocyte elastase
$360,427 (7/90-6/93)

3. Johnson, Paul — Cardiovascular
Thrombin function/inhibition in tobacco-related diseases
$592,356 (7/90-6/93)

4. Pollart, Daniel — Cancer
Novel hypoxic cytotoxins to enhance lung cancer radiotherapy
$152,412 (7/91-6/92)

5. Ward, Marcia — Intervention
Laboratory & ambulatory assessment of smoking withdrawal
$385,657 (7/90-6/92)

6. Webster, Keith — Cardiovascular
Roles of hypoxia, nicotine & camp in ischemic heart failure
$711,742 (7/90-6/93)

AWARD # RT294 AWARD PERIOD 3 years 7/1/90 to 6/30/93

PRINCIPAL INVESTIGATOR Charles K. Hiebert

INSTITUTION SRI International

TITLE OF PROJECT Novel Benzoxazinone Inhibitors to Human Leukocyte Elastase

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Tobacco smoke induces a variety of chronic lung ailments, including emphysema. Like many other irritants, tobacco smoke activates the release of the serine protease human leukocyte elastase (HLE), an important component in the mechanism by which the body clears foreign proteins and other substances from the lung. HLE activity is regulated by the release of an endogenous inhibitor, α1-antitrypsin. Tobacco smoke inactivates α1-antitrypsin by oxidizing the molecule, and the resulting unimpeded HLE release leads to widespread lung tissue damage and eventually to emphysema.

One approach to the treatment of emphysema is to restore the protease-inhibitor balance through the use of potent low-molecular-weight inhibitors to HLE. Analogs of 4*H*-3,1-benzoxazin-4-one act as mechanism-based inhibitors of HLE and are thus specific for serine proteases. Our approach is to incorporate fragments characteristic of the natural peptide substrates as substituents on the 4*H*-3,1-benzoxazin-4-one ring as a method of increasing the specificity and potency of this class of inhibitor for HLE as opposed to other serine proteases. During the first year, we focused on synthesizing three prototype inhibitors in which an amino acid side chain is attached to the 6-position of the 4*H*-3,1-benzoxazin-4-one ring. The synthesis of each of these prototypes is near completion. During this research period we developed methodologies that will be applied to the synthesis of numerous new inhibitors in the next year. All compounds will be tested for their potency and specificity for HLE.

2023471098

Source: https://www.industrydocuments.ucsf.edu/docs/fbv0000

AWARD # RT303 AWARD PERIOD 3 years 7/1/90 to 6/30/93

PRINCIPAL INVESTIGATOR Charles K. Hieben

INSTITUTION SRI International

TITLE OF PROJECT Peptidyl Phosphonate Inhibitors of Human Leukocyte Elastase

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Tobacco smoke is believed to be the primary agent responsible for the induction of numerous chronic pulmonary disorders, including emphysema. In addition to promoting the release of the proteolytic enzyme human leukocyte elastase (HLE), tobacco smoke inactivates α1-antitrypsin, the regulatory inhibitor of HLE, through oxidation of an essential methionine residue. This process results in a protease-inhibitor imbalance, which leads to an unimpeded release of HLE. While HLE is important in clearing foreign material from the lung, excessive levels produce damage to lung tissues, which eventually progresses to the disease state of emphysema.

One approach to the treatment of emphysema is to reestablish the protease-inhibitor balance through the use of synthetic inhibitors of HLE. Aminoalkylphosphonate esters have been shown to be mechanism-based inactivators of serine proteases similar to HLE without inactivating serine esterases. Our approach is to synthesize substrate analogs of HLE inwhich the amino acid whose carboxyl group is involved in the cleavage step is replaced by the appropriate aminoalkylphosphonate ester. The resulting compound should demonstrate high potency and specificity for HLE over other serine proteases. During this first research period, we prepared a number of esters of the desired aminoalkylphosphonate and substrate fragments that incorporate moieties for enhanced bioavailability in the lung. These esters and fragments are now being coupled to give the proposed target compounds.

AWARD # 1RT 391 AWARD PERIOD July 1 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Paul H. Johnson

INSTITUTION SRI International

TITLE OF PROJECT Thrombin Function/Inhibition in Tobacco-Related Diseases

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Thrombin is the key enzyme that functions in regulating blood coagulation. It also affects the function and proliferation of cells. Thrombin plays an important role in several life-threatening diseases including atherosclerosis (and associated complications such as coronary thrombosis), stroke, pulmonary embolism, and tumor cell metastasis (the ability of cancer cells to spread). Existing evidence strongly links the use of tobacco products with an increased risk of cardiovascular disease and cancer.

The ability to inhibit thrombin selectively and specifically, offers an important new therapeutic approach to the treatment of cardiovascular disease and metastatic cancer. Hirudin, a naturally occurring protein comprised of a chain of 65 amino acids, is the most potent and most specific known inhibitor of thrombin. Hirudin has demonstrated great therapeutic potential and offers a unique approach to determining the regions of thrombin that are important for its activity and for studying the function of thrombin in disease processes.

The specific goals of this year's work have been to understand how the binding of various modified forms of hirudin to thrombin affects its function and to develop hirudin analogs with improved properties for therapeutic and diagnostic applications. We have demonstrated that structural changes within the first five amino acid residues of hirudin dramatically alter its ability to inhibit thrombin. Analyses of several genetically engineered forms of hirudin indicate that the amino acid tyrosine at position 3 of hirudin binds in a particular part of the active-site region of thrombin. The significant effect of certain modifications on decreasing hirudin activity suggests that alteration of the amino-terminal (beginning) segment can destabilize the interaction of other regions of hirudin with thrombin. In addition, chemical modification studies indicate that specific amino acids at both end regions of hirudin interact with thrombin. We have developed one modified form of hirudin that has increased thrombin inhibition potency and may prove therapeutically useful.

AWARD # RT547 AWARD PERIOD 7-1-90 to 6-30-91

PRINCIPAL INVESTIGATOR Marcia M. Ward, Ph.D.

INSTITUTION SRI International

TITLE OF PROJECT Laboratory and Ambulatory Assessment of Smoking Withdrawal

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objectives of this project are to investigate the physiological, cognitive, and emotional changes that occur during smoking withdrawal and the extent to which these changes predict relapse. To meet these goals, a pilot study intensively studied 16 quitters (6 males and 10 females, mean age = 52, mean amount smoked = 37 cigarettes per day) daily for the first week following smoking cessation. The participants completed three withdrawal symptom scales twice daily. On alternate days, they wore ambulatory monitors that measured heart rate (HR) and blood pressure (BP) three times an hour while the subjects were awake and once an hour during sleep. At each awake reading, the subjects completed a diary of posture, activities, and withdrawal symptoms. Results indicated that physical activity levels were stable across days. Hourly ambulatory HR and BP levels were consistent across days following a marked circadian/activity cycle. The noticeable exception was a substantial HR decline of 12 bpm over the first 6 hours following cessation. Almost all withdrawal symptoms peaked during the first 48 hours after cessation. By 6 months, 55% of these subjects had relapsed. All relapsers were female. Relapsers had lower income, were older, had made more previous quit attempts, and scored higher on an addiction scale of reasons for smoking than did continuing abstainers. The findings from this pilot study have been incorporated into the design of a larger Phase II study, which is in progress. For the Phase II study, 60 quitters will be compared with 30 nonsmokers and 30 continuing smokers. To date, 18 quitters have begun this study. They are wearing ambulatory monitors and completing diaries and withdrawal symptom scales and cognitive testing on three occasions: before cessation, during the first 24 hours following cessation, and 1 month later. Withdrawal symptoms and smoking records are also being completed daily for the first 3 days following cessation and weekly for the first month. The subjects are being weighed and having biochemical verification of abstinence conducted weekly.

AWARD # 1 RT-402 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Keith Webster

INSTITUTION SRI International

TITLE OF PROJECT Roles of Hypoxia, Nicotine, and cAMP in Ischemic Heart Failure

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Suboptimal delivery of oxygen to cells and tissues may result from a variety of physiological and pathological conditions, ranging from prolonged vigorous exercise in skeletal muscle to atherosclerosis and restricted vascularization of solid tumors. These states may be promoted and are compounded by reduced oxygen absorption by lung capillaries and lower transport capability of blood caused by tobacco smoking. In the heart, this condition may be further exacerbated by nicotine, which, by stimulating the release of catecholamines from the adrenal medulla and other sites, increases myocardial oxygen demand. Because myocardial ischemia, usually the leading cause of mortality in Western populations, smoking, is directly or indirectly the leading cause of mortality in Western populations. the regulation of heart function under hypoxia has been intensively studied. *In vivo*, ischemia/hypoxia may be extreme and abrupt, as in arterial thrombosis, or, more commonly, limited and chronic, as in the gradual narrowing of arteries during the progression of atherosclerosis. In the heart, both conditions result in depressed contractility. In acute ischemia, reduced contractility has been attributed to waste metabolite buildup or depletion of energy reserves. In chronic hypoxic conditions, oxygen delivery may be enough to maintain tissue viability but contractility is impaired. The term hibernating myocardium has been given to this condition. The signals that regulate reduced contractility and survival in this setting have not been identified.

In our TRDRP-supported studies, we have new evidence that the intracellular second messenger, cyclic AMP (cAMP), may mediate myocardial hibernation. Spontaneously beating neonatal rat heart cells exposed to chronic, moderate hypoxia exhibited a progressive decline in intracellular cAMP. This coincided with a cascade of effects on putative cAMP-mediated cellular functions, including contractility, calcium flux, and gene expression. When cAMP levels were maintained under hypoxia by adding an adenylate cyclase agonist and phosphodiesterase (PDE) inhibitor, these effects were largely reversed but the cells died. These results suggest that cAMP can mediate multiple adaptive responses that protect heart and possibly other cells against prolonged periods of hypoxia. Furthermore, the results provide, seemingly for the first time, an explanation for the clinical toxicity of a class of congestive heart failure drugs with PDE-inhibitory properties that were widely promoted in the 1980s and in fact are still in use. As a corollary to this explanation, the results provide a foundation for a new model screening system for new potentially therapeutic compounds that is expected to reduce the need for first-level animal testing.

2023471099

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

3

Grant Awards by Institution

Stanford University

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

13 $5,736,656

b) The subject of research grants by academic discipline:

Cancer	= 2
Cardiovascular Disease	= 2
Epidemiology	= 1
General Biomedical Science	= 2
Public Health, Public Policy, and Economics	= 1
Pulmonary Disease	= 1
Tobacco-Use Prevention, Intervention, and Cessation	= 4

c) The relationship between State and Federal funding for tobacco research:

Other State	= 0
Federal	= 338,659

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

3 $1,270,730

g) The number and species of animals used in research:

Mice	= 500/year
Rabbits	= 100/year
Rats	= 50/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

3 $656,087

Grant Recipient(s):

1. Adler, Kent — Cancer
Drug resistance during induction chemotherapy for lung cancer
$35,046 (7/90-6/91)

2. Butcher, Eugene — Pulmonary
Molecular mechanisms of leukocyte traffic to the lungs
$348,150 (7/90-6/93)

3. DeBusk, Robert — Intervention
Hospital-based intervention to prevent smoking relapse
$698,868 (7/90-6/93)

4. Dzau, Victor J. — Cardiovascular
Vascular-response to injury: potentiation by nicotine
$576,741 (7/90-6/93)

5. Feldman, David — Gen Biomed
Cigarette smoking, steroidogenesis & steroid receptors
$320,944 (7/90-6/92)

6. Fortmann, Stephen — Intervention
Relating tobacco access and consumption among youth
$489,771 (7/91-6/94)

7. Holman, Halsted R. — Pub Health
Self-management for tobacco-related chronic diseases
$1,055,960 (7/90-6/93)

8. Jackson, Christine — Intervention
Family intervention to prevent smoking: preliminary studies
$160,271 (7/90-9/91)

9. Lawn, Richard — Cardiovascular
Apolipoprotein(a) and cardiovascular disease
$590,733 (7/91-6/94)

10. Lewis, Alexander — Cancer
Glutathione transferase in lung cancer: transfection studies
$75,600 (7/90-6/92)

11. Spiegel, David — Intervention
Effect of single-session hypnosis on smoking cessation
$584,845 (7/91-6/94)

12. Switzer, Paul — Epidemiology
Statistics of tobacco smoke exposure
$455,271 (7/91-6/94)

13. Tribble, Diane — Gen Biomed
Cigarette smoke exposure & antioxidant activity in blood
$344,456 (7/90-6/93)

2023471100

AWARD # FT 52 AWARD PERIOD July 1, 1990 - June 30, 1992

PRINCIPAL INVESTIGATOR Kent M.J. Adler, M.D.

INSTITUTION Stanford University Medical School

TITLE OF PROJECT Drug Resistance During Induction Chemotherapy for Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project has two major objectives: (1) Evaluate the effectiveness of etoposide, ifosfamide and cisplatin (VIP) chemotherapy in patients with locally and regionally advanced non-small cell lung cancer and assess the feasibility of achieving a potentially curative surgical resection after VIP. (2) Compare the levels of two factors associated with chemotherapeutic drug resistance in tumor specimens before and after chemotherapy and assess whether the level of expression of either factor or the change in the level of expression correlates with response to treatment. Patients are treated with 3-4 cycles of VIP, followed by surgery, radiation therapy and, finally, by two more cycles of VIP. Tumor specimens are obtained prior to chemotherapy (when possible) and at surgery. To date, 4 patients have been enrolled. Chemotherapy toxicity has consisted of suppression of the white blood cell and platelet count, hair loss and controllable nausea and vomiting. One patient was unable to undergo surgery due to weight loss and malaise during chemotherapy. All patients had tumor shrinkage during VIP, with three having marked reduction in tumor size. Two patients have had surgery, one with complete removal of minimal remaining tumor and one with partial removal of residual cancer. One patient is awaiting surgery. All patients are alive and their cancers have not regrown with follow-up of 4 - 19 months. Progress toward the second objective has been slow due to technical problems in obtaining adequate specimens. Part of the problem stems from the early effectiveness of VIP chemotherapy: one of the patients who had surgery had such a minimal amount of tumor remaining that analysis of the specimen was impossible. Recently, I have initiated a new study attempting to reverse drug resistance in patients with small cell lung cancer. Cyclosporine, a potent inhibitor of p-glycoprotein-mediated multidrug resistance is used in combination with the standard chemotherapeutic agents doxorubicin, etoposide and vincristine (C-DEV). Resistance to these three drugs is mediated, at least in part, by p-glycoprotein. All patients have relapsed or refractory small cell lung cancer. To date, 3 patients have been enrolled on study. Results are too early to evaluate.

Summary: The preliminary data from the preoperative VIP in non-small cell lung cancer study suggest that the regimen can be administered with acceptable toxicity. The early responses are very encouraging. However, the patients enrolled are too few and the follow-up too short to draw any conclusions as to the efficacy of this treatment approach. The C-DEV study in drug resistant small cell lung cancer is an exciting new approach to the treatment of cancer. It is one of the first clinical trials attempting to reverse drug resistance in a solid tumor. Accrual for both studies continues. If the results of either study are positive, I anticipate a confirmatory study within the Eastern Cooperative Oncology Group followed by a randomized trial comparing the new approach to standard treatment.

AWARD # 1RT456 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Eugene C. Butcher, M.D.

INSTITUTION Stanford University

TITLE OF PROJECT MOLECULAR MECHANISMS OF LEUKOCYTE TRAFFIC TO THE LUNGS

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

One of the most important goals of our project is to explore the molecular mechanisms of neutrophil traffic to the lungs. Recent studies have indicated that neutrophils can be recruited to pulmonary tissue through both β2 integrin-independent as well as dependent mechanisms, where as in other tissues β2 integrin-dependency is the rule. During the past year, we have made substantial progress in understanding both the role of the β2 integrins and of the lectin homing receptor (LECAM-1) in neutrophil interactions with activated endothelial cells in inflamed tissues. First, we have shown that one of the monoclonal antibodies we have produced against the human homing receptor LECAM-1 crossreacts with LECAM-1 in the rabbit. In collaboration with Karl Arfors' Microcirculation Unit (La Jolla Institute), we have found that this anti-LECAM-1 antibody inhibited the earliest "rolling" interaction of neutrophils with inflamed venules: in contrast, antibodies to the β2 integrins have no effect on this early interaction, but instead inhibit subsequent activation-dependent arrest and stable adhesion leading to extravasation. This led us to propose a multi-step model of neutrophil extravasation, in which initial interaction is mediated by the activation-independent adhesion molecule LECAM-1, permitting neutrophils to be activated by the local environment of the inflamed venule, leading subsequently to activation-triggered adhesion via the integrins. This model has fundamental implications for understanding of leukocyte-endothelial cell interactions. For example, in the case of pulmonary extravasation in which, in many instances, the β2 integrins appear not to be critically involved, one may hypothesize either that LECAM-1-mediated adhesion may be adequate to arrest neutrophils, or more likely that a distinct activation-dependent adhesion mechanism is involved. The availability of an anti-LECAM-1 MAb in the rabbit will allow us to explore these questions in well established rabbit models of pulmonary injury and inflammation.

At the molecular level, we have found that neutrophil LECAM-1 mediates rolling interactions with inflamed endothelial cells in large part through presentation of neutrophil carbohydrate ligands to the vascular lectins ELAM-1 and/or GMP140. Based on these studies, it will be important to explore the role of the expression of these vascular lectins (which in the case of ELAM-1 during chronic inflammation displays substantial tissue selectivity) in the lung, and to ask whether the leukocyte and vascular lectins play important roles in pulmonary as in other models, or whether distinct mechanisms are involved.

AWARD # 1RT81 AWARD PERIOD 7/1/91 - 6/30/92

PRINCIPAL INVESTIGATOR Robert F. DeBusk, M.D.

INSTITUTION Stanford University

TITLE OF PROJECT Hospital-based intervention to prevent smoking relapse

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Although hospital smoking bans afford an important opportunity to foster smoking cessation, mechanisms are lacking to capitalize on this opportunity. This research project provides a nurse (RN)-managed intervention to prevent smoking relapse among hospitalized patients who have undergone enforced abstinence from smoking. Among smokers admitted to the medical services of 2 large Kaiser-Permanente hospitals in the San Francisco Bay Area, those who express a willingness to participate in the study will be randomized to receive the RN-managed relapse prevention intervention (GP2, n=333) or not to receive it (GP1, n=333). Physicians caring for Group 2 patients will provide a brief, standardized message about the health consequences of smoking and the benefits of quitting and will convey their support of the RN-managed intervention. Research nurses will train Group 2 patients to avoid smoking in their individual high-risk situation and during the following 12 weeks will telephone patients 4 times at home to ascertain smoking status, problem-solve, and provide additional information and support. Group 2 patients who relapse will be offered a second office-based counseling session with the nurse and 2 RN-initiated followup telephone contacts. The primary outcome measure, obtained in patients of both groups at one year, is smoking cessation rate confirmed by measurement of salivary cotinine. The project is designed to increase the cessation rate from 20% among patients receiving usual care to 30% or more among patients receiving the RN-managed intervention. The attributes of the RN-managed intervention are of proven efficacy: multiple components, face to face counseling by the nurse and the physician and multiple contacts over a sustained period.

AWARD # 1RT215 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR VICTOR J. DZAU, M.D.

INSTITUTION STANFORD UNIVERSITY

TITLE OF PROJECT "Vascular-Response to Injury: Potentiation by Nicotine"

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting form the work. Limit the abstract to a space 6" by 5.5".

Alterations in vascular reactivity and growth control participate in the pathogenesis of vascular occlusive disease in response to vascular injury. These abnormalities are major complications which limit the success of angioplasty, endarterectomy or venous bypass grafts. These pathological responses to vascular injury are further potentiated in patients who use tobacco. Nicotine is a major component of tobacco that may play an important role in promoting vascular diseases. Accordingly, we will examine the effects and mechanisms of chronic nicotine exposure on altered vascular reactivity and vascular structure in noninjured and injured vessels. Moreover, we will examine the effect of nicotine on the growth and structure of vascular smooth muscle cells in culture. Therefore, our specific aims are to 1) examine the factors *in vivo* which regulate vascular reactivity, 2) examine the factors which regulate the growth and structure of vascular smooth muscle cells *in vivo* and *in vitro*, and 3) examine the effect of nicotine on the vascular reactivity *in vivo* and growth *in vitro* and *in vivo*.

Over the past year, we have been defining the factors which regulate the growth of vascular smoooth muscle cells in culture. Our results indicate that the basal and induced growth of these cells is regulated, in part, by the autocrine production of growth factors. These three factors differ in their effects, inducing different degrees of hyperplasic (i.e., increase in cell number) or hypertrophic (i.e., increase in cell size) growth. We hypothesize that the relative levels of induction of these factors will regulate the response of the smooth muscle cells to various stimuli. The effect of nicotine on the expression and action of these factors is being examined.

We are also examining the mechanism of the neointimal proliferation following vascular injury, particularly the role of angiotensin in this response. Our results confirm that angiotensin blockade in rats using converting enzyme inhibitors or selective angiotensin receptor antagonists will block the neointimal proliferation. Moreover, the neointima expresses both angiotensinogen (the substrate for angiotensin) as well as angiotensin converting enzyme (the enzyme responsible for the production of angiotensin). Thus the smooth muscle cells growth may be regulated by the autocrine production of angiotensin. The effect of nicotine on these expressions is currently being examined.

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

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AWARD # 1RT 186 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR David Feldman, M.D.

INSTITUTION Stanford University

TITLE OF PROJECT Cigarette Smoking, Steroidogenesis and Steroid Receptors

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project was designed to examine the hypothesis that nicotine and related substances present in cigarette smoke might cause increased risk of cardiovascular disease, cancer, and osteoporosis by altering the steroid hormone balance in the smoker. We proposed two possible mechanisms by which nicotine and its metabolites could cause an impact on steroid hormone levels and/or action. The first proposed mechanism was that nicotine might inhibit critical cytochrome P450 enzymes in the steroidogenic pathways causing inhibition of the synthesis of estrogens, androgens, glucocorticoids or 1,25 dihydroxyvitamin D_3 [1,25(OH)$_2$D$_3$]. Decreased levels of protective hormones might predispose to increased risk of disease. Alternatively, inhibition of one steroidogenic pathway could lead to shunting of substrates into other pathways causing hormone excess and also increasing disease risk. The second proposed mechanism was that nicotine and related substances might directly bind to the receptors for these steroid hormones (ER, AR, GR, and VDR), and thereby inhibit the actions of the steroids at the target tissue level.

Our initial experiments were directed at the second proposed mechanism. A human breast cancer cell line (MCF-7) that can be grown in culture is known to possess all four receptor subtypes: ER, AR, GR, and VDR. Radio-ligand binding assays were developed to quantitate each of these receptor types using [^{3}H]estradiol, [^{3}H]dihydrotestosterone, [^{3}H]dexamethasone, and [^{3}H]1,25(OH)$_2$D$_3$. Experiments were then performed to determine whether nicotine, cotinine, or anabasine were able to compete with any of these radioligands for specific receptor binding sites. All of the experiments performed to date have been negative. The constituents of cigarette smoke do not appear to directly bind to any of these four steroid receptors. These results indicate that nicotine does not cause actions on cells by occupancy of steroid hormone receptors. The next experiments will be directed at the other proposed mechanism, that of inhibition of steroidogenic pathways. This possibility will be evaluated as described in the grant proposal.

AWARD # 1 RT3 AWARD PERIOD 7-1-90 - 6-30-91

PRINCIPAL INVESTIGATOR Christine Jackson, Ph.D.

INSTITUTION Stanford University

TITLE OF PROJECT Family Intervention to Prevent Smoking: Preliminary Studies

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this research is to conduct preliminary studies leading to the development of a family-based, early socialization program for smoking prevention. The Year 1 objectives for the project, and the work completed to date, are described here.

Objective 1: Define and operationalize variables relevant to the study of children, parents, family socialization processes and cigarette smoking. A 350 article bibliography has been compiled and reviewed, and a conceptual model has been developed. The model provides new insights into family variables that put children at high risk for smoking, and it indicates that there are multiple developmental profiles which should be investigated to determine their contribution to smoking onset.
Objective 2: Develop research instruments to measure the variables in the model. Two survey instruments have been developed: one, a self-report survey for children in grades 3 - 8; the other, a teacher survey to measure academic and social competencies in children.
Objective 3: Conduct a field test of the instruments. An initial sample of 950 students from four elementary schools and two middle schools was completed 5.24.91. Preliminary analyses are underway.
Objective 4: Prepare a manuscript describing the concepts underlying the early socialization approach and the measures developed to study this approach. A manuscript titled *The Preparation Phase of Smoking: A Viable Target for Preventive Intervention* is in preparation.

AWARD # RT156 AWARD PERIOD 1 July 1990 - 30 June 1991

PRINCIPAL INVESTIGATOR Waleed R. Holman, M.D.

INSTITUTION Stanford Medical School

TITLE OF PROJECT Self-Management for Tobacco-Related Chronic Diseases

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This is a long-term project designed to create and test a learning experience concerning Self-Management for Tobacco-Related Chronic Diseases. It is hypothesized that, after the learning experience, participants with four chronic diseases (arthritis, lung disease, coronary artery disease with angina and stroke with normal mentation) will (1) understand their disease and its treatment better, (2) play a more active role in disease management, (3) experience a diminution in certain major symptoms, (4) increase their physical and social activities and (5) reduce their use of health care services. The first year of the project has been devoted to establishing the content of the learning experience, developing the evaluation instruments, and field testing the early instruments. These results are recounted in the technical analysis portion of this progress report. There are no experimental results to report at this time.

AWARD # 1 FT 38 AWARD PERIOD 07/01/90 to 06/30/91

PRINCIPAL INVESTIGATOR Alexander D. Lewis

INSTITUTION Stanford University

TITLE OF PROJECT Glutathione Transferase in Lung Cancer: Transfection Studies

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Lung cancer is the most prevalent form of cancer found among adults in the United States with approximately 10% of this total in the State of California. Smokers are predisposed to lung cancer and the risk increases with the amount of tobacco smoke inhaled. Individual characteristics may influence the susceptibility of the smoker to lung cancer. In this regard the removal of toxic chemicals of tobacco smoke by protein factors known as enzymes, and called the glutathione-s-transferases (GST's), are thought to play an important role. Another aspect of lung cancer which is of interest, is the clinical non-responsiveness of many of the lung tumor types to chemotherapy. The reason for this difference in response is still unclear. However, one of the postulations is that the GST's, which are involved in the removal of certain anticancer drugs, may be present at different levels in different lung tumor types and influence the response of the tumor to chemotherapy. The objectives of my project, therefore, are to study the function of GST's in cells which have been genetically altered (transfected) with genetic material (DNA) coding for the enzymes, and also to examine the presence of these GST DNA's in clinical lung cancers. Ultimately, this information could benefit the people in the state of California by providing evidence for the role of GST's as a factor which can influence individual susceptibility to lung cancer, and also for predicting the response of lung cancer patients to chemotherapy.

The most significant finding arising from the work so far has been the development of an extremely sensitive assay (for the three main gene families of GST's) called the Polymerase Chain Reaction (PCR), which can amplify very small amounts of DNA. This method has been validated for sensitivity and accuracy in human tumor-derived cell lines, before the extension of the study to clinical lung tumor samples. The other main finding concerns the transfection of DNA, coding for a human GST enzyme, which corrected the defect in a tumor cell line that showed sensitivity to a chemotherapeutic agent, bleomycin. These studies are also in the process of being expanded to look at the effect of other GST genes and chemotherapy response.

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Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

AWARD # 1KT 106 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Diane L. Tribble, Ph.D., R.D.

INSTITUTION Stanford University

TITLE OF PROJECT Cigarette Smoke Exposure and Antioxidant Activity in Blood

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Radical-initiated oxidative processes have been implicated in the development of atherosclerosis, the underlying cause of coronary heart disease (CHD). Radicals and radical-generating compounds in cigarette smoke may contribute to increased CHD risk among smokers by depleting protective antioxidants and initiating atherogenic oxidative processes. The present studies aim to examine effects of chronic cigarette smoke exposure on antioxidant levels in blood, and to explore mechanisms by which antioxidant depletion may accelerate atherosclerosis.

To identify and describe differences in antioxidant activity as a function of smoke exposure, dietary and plasma antioxidants (e.g., ascorbate, beta-carotene, Alpha-tocopherol) are being measured in a cross-sectional sample of adult females comprising 50 nonsmokers, 50 active smokers and 50 passive smokers. Other measured variables include indices of smoke exposure (e.g., carbon monoxide expiration) and plasma lipoprotein cholesterol levels.

Funding for this study began July 1, 1990. The first 8 months were devoted to setting up laboratory methods. Participant recruitment was initiated in March, 1991. To date, 75 women have been screened for eligibility on the basis of age, menopausal status, and self-reported smoke exposure. Of these, 45 have been deemed eligible, and 40 have participated, including 27 nonsmokers, 5 active and 8 passive smokers. We will continue recruitment, with intentions of completing this phase of the project by March, 1992, after which we will complete all laboratory analyses, and will begin data analysis and reporting.

To explore whether differences in antioxidant levels may affect the atherogenicity of plasma lipoproteins, we also have initiated a subproject (in collaboration with Dr. Ronald M. Krauss at U.C.-Berkeley) examining the response of isolated low-density lipoprotein (LDL) subfractions to oxidizing conditions in vitro. Small, dense LDL subclasses, which are known to be increased in smokers, were found to be more susceptible to oxidation than large, buoyant LDL subclasses. Surprisingly, intrinsic differences in oxidative susceptibility were not explained by differences in lipoprotein antioxidant levels. Future studies will investigate whether enrichment with antioxidants is effective in reducing LDL oxidative susceptibility, and whether the effects of enrichment vary among LDL subclasses.

2023471103

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

University of California, Berkeley

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

12 $3,691,030

b) The subject of research grants by academic discipline:

Cancer	= 1
Epidemiology	= 1
General Biomedical Science	= 3
Public Health, Public Policy, and Economics	= 4
Pulmonary Disease	= 3

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

4 $839,642

g) The number and species of animals used in research:

Rabbits	= 11/year
Rats	= 277/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

2 $884,541

Grant Recipient(s):

1. Ashby, Matthew — Gen Biomed
Post-translational processing of ras and yeast a-factor
$70,000 (7/91-6/93)

2. Brooks, George — Pulmonary
Effects of smoking on metabolism during rest and exercise
$504,382 (7/90-6/93)

3. Bruvold, William — Pub Health
Meta-analysis of prop 99 competitive grant funded projects
$233,468 (7/90-6/93)

4. Eskenazi, Brenda — Epidemiology
Cotinine levels in pregnant women & child development
$330,068 (7/90-6/93)

5. Hu, Teh-Wei — Pub Health
The economic effects of California cigarette taxation
$458,628 (7/90-6/93)

6. Lambert, Nadine M. — Pub Health
Prospective study of cigarette smoking & behavior dysfunction
$500,370 (7/90-6/93)

7. Miller, Sheldon — Pulmonary
The effects of smoke on fluid transport across trachea
$395,115 (7/90-6/93)

8. Nazaroff, William — Gen Biomed
Controlling exposure to environmental tobacco smoke
$205,357 (7/90-6/93)

9. Packer, Lester — Pulmonary
Tobacco smoke, free radicals, antioxidants and disease
$319,483 (7/90-6/93)

10. Rine, Jasper — Cancer
Suppression of oncogenic ras mutations
$380,159 (7/90-6/93)

11. Sugarman, Stephen D. — Pub Health
Tobacco and its related diseases: law, policy and politics
$224,000 (7/90-6/92)

12. Trueblood, Cynthia — Gen Biomed
Protein prenyltransferases required for ras function
$70,000 (7/91-6/93)

2023471104

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

AWARD # RT 327 AWARD PERIOD July 1, 1990-June 30, 1991

PRINCIPAL INVESTIGATOR George A. Brooks

INSTITUTION University of California, Berkeley

TITLE OF PROJECT Effects of Smoking on Metabolism During Rest and Exercise

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

In our first year we focused our efforts in two areas. First, we have worked hard to obtain the most advanced equipment necessary for human, stable isotope research. Fortunately for all concerned, the vendor introduced a new generation of gas chromatograph-mass spectrometer (GC-MS) which we were able to obtain at a significant discount. The negotiations and limited availability of the GC-MS has necessitated a delay in delivery, but the device is currently being installed. Thus, we enter the second year of funding having established an analytical facility which may become a Regional Center for Tobacco-Related and other Stable Isotope Research. Additionally, savings realized in purchase of the GC-MS system has allowed purchase of equipment applicable to metabolic studies on pregnant women, a major goal of our proposal.

Secondly, our scientific efforts have focused on the mechanisms by which smoking induced limitations in circulatory oxygen transport affect the body's fuel utilization. In collaboration with others (and in absence of our GC-MS system) we have shown that low oxygen (hypoxia) increases carbohydrate utilization in humans.

We have shown that acute (sudden) exposure to hypoxia (low oxygen in inspired air) causes a shift towards increased blood glucose (sugar) utilization during prolonged moderate intensity exercise. Additionally, we have shown that acclamatization to hypoxia results in increased glucose utilization even at rest. Moreover, after acclimatization to hypoxia, glucose utilization is greatly elevated during exercise. Finally, our measurements of the neuro-endocrine responses to exercise and hypoxia indicate that the sympathetic nervous system likely plays an important role.

We have learned much this year about how to utilize stable isotopes and how to apply them to studies of human metabolism during exercise and hypoxic stresses.

AWARD # 1RT 465 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Brenda Eskenazi

INSTITUTION University of California, Berkeley

TITLE OF PROJECT Cotinine Levels in Pregnant Women and Child Development

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this project is to determine whether active smoking and/or passive exposure to environmental tobacco smoke (ETS) by pregnant women has adverse effects on the growth and neurodevelopment of their children. The participants include 4379 women who received prenatal care at East Bay Kaiser Permanente Hospital facilities between 1964 and 1967 and were enrolled in the Child Health and Development Studies. Exposure to tobacco smoke is being assessed by measurement of cotinine, a biomarker and metabolite of nicotine, in the sera collected in the later part of the woman's pregnancy. The cotinine levels are being linked to information already obtained by questionnaire and on medical record including the women's smoking behavior, socio-demographic characteristics, child's birthweight, child's height, and neurodevelopmental measurements at age 5. Cotinine levels have already been determined for approximately 1800 women, and these levels have been linked to questionnaire and medical record data for a pilot sample of 505 women. Levels of cotinine in smokers were found to be similar to the range of values found in women who smoke today. The overall mean values of cotinine were similar for black and white subjects (approximately 138 ng/ml). Cotinine levels were found to increase with self-reported cigarette consumption. A small negative linear relationship was found between serum cotinine and birthweight, with birthweight decreasing an average of 0.026 ounces for every 1 ng/ml increase of serum cotinine (p=0.03). We are presently examining the relationship of growth at age 5 and mother's smoking habits during pregnancy in black and in white children. Preliminary results demonstrate that white children whose mothers smoke are about 1 cm shorter than children of nonsmokers, and this effect is more profound in white children than black children. In contrast, a preliminary analysis of the relationship between self-reported smoking consumption and neonatal mortality shows that mortality rates are similar for white infants of smokers and non-smokers, but mortality rates are considerably higher for black infants of smokers than non-smokers.

AWARD # RT-13 AWARD PERIOD 7-1-90 to 6-30-93

PRINCIPAL INVESTIGATOR William H. Bruvold

INSTITUTION University of California, Berkeley

TITLE OF PROJECT A Meta-analysis of Proposition 99 Competitive Grant Funded Projects

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The project has four objectives as noted below.

1) To systematically analyze results from the published literature on school-based programs designed to prevent adolescent smoking.

2) To systematically analyze results from the published literature on community-based programs designed to prevent smoking and to foster cessation.

3) To systematically analyze results from Proposition 99 competitive grant funded school-based programs designed to prevent adolescent smoking, sponsored by the California Department of Education.

4) To systematically analyze results from Proposition 99 competitive grant funded community-based programs designed to prevent smoking and foster cessation, sponsored by the California Department of Health Services.

To date results have been obtained for objective 1) which show that school-based programs having a social reinforcement orientation have the most effect, those having social norms or development orientations have intermediate effects, and those having a rational orientation the least effect.

AWARD # RT 12 AWARD PERIOD 07/01/90-06/30/93

PRINCIPAL INVESTIGATOR Teh-wei Hu

INSTITUTION University of California, Berkeley

TITLE OF PROJECT THE ECONOMIC EFFECTS OF CALIFORNIA CIGARETTE TAXATION

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This study analyzes the effects of the 1989 California cigarette tax increase on consumption of cigarettes, using both cross-section and time-series data from California, with further evidence for comparison from surrounding states. Five data sets have been collected, including aggregated monthly and annual time series for California, a panel of data for 11 Western states, and two cross section samples of data on individuals within California, collected for years before and after the tax increase. Statistical analysis has begun on all data sets except for one, and two working papers have been completed. So far, several important conclusions have resulted. First, the cigarette tax increase of 1989 had a strong effect in reducing consumption: after adjustment for seasonal variation and trend-related changes, we find that as of January, 1989, cigarette consumption was reduced by 1.22 cigarettes per capita per month compared to what it would have been in the absence of the tax (however, the effect of the tax appears to decline over time; by December, 1990, consumption was only .64 packs per month per capita below the long-term trend). Furthermore, even after controlling for the effects of increases in antismoking regulations, income, and other social changes affecting smoking trends, the price of cigarettes was both strongly affected by the tax and strongly affected consumption. Our results show that at the time of the tax, we find that (all other things equal) a one-per cent increase in the price of cigarettes reduces consumption by about .6 to .7 per cent. Preliminary evidence on the price responsiveness in adjoining states further supports this conclusion. Our results also indicate that smokers reduced consumption quickly in response to increased prices: there was little if any lag. Further analysis of the effects of the tax is now underway, pursuing several paths. The first concerns the effects of the tax by demographic group in California (sex, age, ethnicity, income). A second research path concerns the way in which the reduction in consumption has been achieved, that is, the extent to which it stems from quitting on the part of existing smokers versus simply cutting back. Third, we are investigating the behavior of the tobacco companies in passing on the tax: we know that prices rose as a result of the tax, but it is important to study this effect in more detail. Finally, we plan to integrate all this evidence to achieve a full picture as to what the tax increase of 1989 did to cigarette consumption in California, and what (if any) feedback effects this may have on health levels.

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Source: https://www.industrydocuments.ucsf.edu/docs/jjv0000

3

Grant Awards by Institution

AWARD NO. [illegible] AWARD YEAR 1 XX 2 ___ 3 ___

PRINCIPAL INVESTIGATOR Nadine M. Lambert

INSTITUTION University of California at Berkeley

TITLE OF PROJECT Prospective Study of Cigarette Smoking Behavior Dysfunction

Please summarize, in language understandable to an educated lay person, the objectives of this project and the progress to date toward achievement of the specific aims. Print the abstract in the box

The research on Prospective Study of Cigarette Smoking and Behavior Dysfunction was designed to cover two major phases of prospective longitudinal inquiry. We have made considerable progress in achieving the goals for this period for both Phase 1 and Phase 2 of the project.

The first phase, covering the first two years of support, is dedicated to a prospective study of the onset of smoking, experimenting with cigarettes, and smoking behavior, and relating these stages of smoking to factors in the life history of each subject.

We have completed those tasks outlined in the project proposal for Year 1. We have created the smoking behavior information at each age of the subjects' lives throughout childhood and adolescence. We have located addresses for 95% of all of our subjects for contact as adults. And we have just about completed the design of the adult interview. Before the end of Year 1 of the project, we should be able to complete a report on our estimate of the prevalence of different types of smoking behavior for children who were asymptomatic and those who were identified and treated for hyperactivity or Attention Deficit Disorder.

Preparation for the second phase, to begin during the second year of the study and to continue in the third year, involved: 1) locating the current address of all of the subjects in the original investigation [N=492 (total with initial parent interviews and subject data) and N=367 (the subset of subjects followed longitudinally from childhood through the end of high school)]; 2) designing the protocol for the adult interview, and; 3) determining the current location of adult subjects and planning strategies for interviewing them.

AWARD # RT 443 AWARD PERIOD 1991-1994

PRINCIPAL INVESTIGATOR Sheldon Miller

INSTITUTION University of California at Berkeley

TITLE OF PROJECT Effects of Smoke on Fluid Transport Across Trachea

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cigarette smoking causes impairment of normal mucociliary clearance in the airways. Ion transport by the airway epithelium, coupled with osmotically obliged fluid movement is thought to be responsible for hydration of the periciliary fluid space that cilia beat in. The maintenance of this sol layer is essential for normal functioning of the mucociliary escalator, yet we know very little about the mechanisms involved in the regulation of its production. Fluid transport has never been directly measured across human airways. The purpose of this project is to directly measure fluid transport across airway epithelial cells from both animals and humans and to learn what mechanisms are important in the regulation of this process. We will also examine the effects of cigarette smoke and specific inflammatory mediators on the transport of fluid across the airway epithelium. This work will hopefully lead to a better understanding of how the fluid lining of the lungs is produced and how cigarette smoking disturbs this process.

We have begun by establishing ongoing relationships with several surgical and autopsy services in order to obtain, on a fairly regular basis, human airway epithelia. We have developed the techniques for culturing airway epithelial cells from bovine and human trachea. Confluent monolayers can be mounted in modified Ussing chambers for short-circuit current and resistance measurements, and some initial experiments have been carried out suggesting that smoke from one cigarette alters ion transport in cultured bovine trachea. We have also modified our present capacitance probe technique for measuring fluid transport so that it can now be applied to cultured cells. Fluid transport across cultured T-84 cells have now been measured for the first time

AWARD # ET 666 AWARD PERIOD 7/90-6/93 (report date: 6/91)

PRINCIPAL INVESTIGATOR William W Nazaroff

INSTITUTION University of California, Berkeley

TITLE OF PROJECT Controlling exposure to environmental tobacco smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Through a combination of laboratory experiments and numerical analysis, we seek to develop an improved understanding of human exposure to environmental tobacco smoke particles. This understanding would serve as a basis both for risk analysis and for engineering efficient measures to limit exposure of nonsmokers in environments in which smoking is permitted. Six tasks were proposed for the three-year project period: (A) determine the size and number of cigarette smoke particles produced by side-stream smoke; (B) investigate the rate of smoke mixing in a single room; (C) investigate the rate of smoke mixing between rooms; (D) evaluate the effectiveness of control techniques; (E) develop numerical modeling tools for assessing exposure to environmental tobacco smoke particles; and (F) conduct field tests to validate the laboratory research. During the first year of research, substantial progress has been achieved on tasks (A), (B), and (E). Regarding Task (A), a method has been developed to determine experimentally the effective emission rate of particles as a function of size from any indoor particle source. In preliminary experiments, the method has been applied to cigarette smoke. For Task (B), an experimental plan has been developed and initiated to investigate the rate of mixing of smoke in a single room. The experiments will be conducted this summer in a full-sized room at the Richmond Field Station's indoor air quality research facility. Concerning Task (E), raising numerical models of particle dynamics in indoor air and regional particle deposition in human lungs have been combined to predict the deposition of environmental tobacco smoke particles in the human lung. As an example, the model has been applied to the case of exposure to smoke issuing from a single cigarette smoked in a 35 m^3 room with average ventilation conditions. An adult nonsmoker residing in the room for 10 hours following cigarette combustion would inhale 350 micrograms of tobacco smoke particles of which about 75 micrograms would deposit in the lung. By comparison, exposure to smoggy Los Angeles air would lead to a total particle deposition of about 300 micrograms in the lung over a ten-hour period

AWARD # RT28 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Dr. Lester Packer

INSTITUTION University of California, Berkeley

TITLE OF PROJECT Tobacco Smoke, Free Radicals, Antioxidants and Disease

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Our objective is to test the hypothesis that highly reactive chemical substances called free radicals, present in cigarette smoke, are a major cause of smoking-related damage. If this were so, then bolstering the antioxidant defense systems, which serve to combat free radicals, might prove to be a powerful approach to preventing or ameliorating smoking-induced damage in active and passive smokers.

Our significant results in the first year are:

1) Establishment of super-sensitive methods of detection of reactive oxygen species (free radicals or free radical products) and the biological products of free radical damage, such as lipid peroxidation and protein oxidation. These will help us accurately measure free radical generation and damage. We have identified oxygen-derived free radical species in cigarette smoke.

2) Development of assays to determine the antioxidant potency of water-and fat-soluble antioxidants. As we learn more about the location and severity of smoking-induced damage, this assay will help us tailor an antioxidant intervention therapy.

3) Determined that nicotine alters the function of neutrophils (cells of the immune system). Using the methods described in 1), we found that nicotine induces a functional alteration in the radical generation of neutrophils, which may contribute to the pathogenesis of smoke-related lung disease.

4) Determined that cigarette smoke causes an enormous amount of plasma protein oxidation, a free radical process. Again, using techniques developed in 1), we have found a 300% increase in plasma protein carbonyls after 3 hours of exposure of plasma to cigarette smoke. We wish to extend this to humans, and to investigate antioxidant interventions to reduce this damage.

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Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

AWARD # 1RT 26 AWARD PERIOD July 1, 1990- June 30, 1991

PRINCIPAL INVESTIGATOR Jasper Rine

INSTITUTION University of California, Berkeley

TITLE OF PROJECT: Suppression of Oncogenic Ras Mutations

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this research is to learn enough basic information to design a drug that will block the action of one of the two most important cancer causing genes in humans. The ras gene, one of these two oncogenes, is present in a mutated form in 20% of all human cancers and contributes in important ways to the cancerous state. Previously we identified a potential Achilles heal to the protein encoded by the ras gene. Specifically, we found that one of the intermediates in the synthesis of cholesterol was attached to the ras protein, and that the attachment of this intermediate was crucial for the function of the protein. We also found that a drug that blocked the synthesis of the intermediate blocked the function of the ras protein. This result implied the potential of a drug-based therapy for some human cancers. However the drug used in these studies is too nonspecific to be useful. Therefore we have investigated the enzyme responsible for placing the cholesterol intermediate on the ras protein. This enzyme offers potential as a good drug target.

So far we have learned that this enzyme consists of two subunits. We have isolated one of the genes and characterized the subunit encoded by that gene. Recently we have identified candidate clones for the gene encoding the other subunit. Together these will enable a thorough understanding of theis enzyme to be obtained. We have also discovered that this enzyme is a member of a family of related enzymes, each with a different target specificity. This result suggests the possibility of target-specific drugs for this family of enzymes. Finally, the attachment of the cholesterol intermediate to the ras protein triggers two further modifications, proteolysis of the tail end of the protein and methylation of the new tail end. We have identified the protease activity is vitro and are beginning a detailed series of experiments to understand what the biological role of the protease activity is.

AWARD #: 1RT 503 AWARD PERIOD: 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR: Stephen D. Sugarman

INSTITUTION: University of California, Berkeley

TITLE OF PROJECT: Tobacco and Its Related Diseases: Law, Policy and Politics

This interdisciplinary research project is in the process of exploring the formation and implementation of various law and public policy initiatives relating to tobacco use. Through a "faculty seminar" format held on the Berkeley Campus, the ten participating scholars (with expertise in law, political science, sociology, business, communications and public health) have been meeting together throughout the year with each other and with experts on a variety of smoking issues from throughout North America. At the same time, each participating faculty member has begun carrying out individual and team research work on the various specific topics of the study. These concern issues such as litigation by smokers against the tobacco companies, tobacco advertising, smoking and insurance, enforcement of smoking control ordinances and employer no smoking policies, and the politics of smoking control legislation. A completed manuscript of the project's findings and analysis is anticipated by the end of the project's planned two year life.

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Grant Awards by Institution

2023471107

Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

University of California, Davis

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

23 $4,565,179

b) The subject of research grants by academic discipline:

Cancer	= 5
Cardiovascular Disease	= 7
Epidemiology	= 2
Pulmonary Disease	= 9

c) The relationship between State and Federal funding for tobacco research:

Other State	= 1,000
Federal	= 42,600

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

13 $2,436,042

g) The number and species of animals used in research:

Dogs	= 25/year
Frogs	= 100/year
Guinea Pigs	= 24/year
Hamsters	= 330/year
Mice	= 370/year
Pigs	= 8/year
Rabbits	= 82/year
Rats	=1,210/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

6 $1,351,197

Grant Recipient(s):

1. Bonham, Ann C. Pulmonary
CNS processing of lung afferent and cigarette smoke inputs
$261,726 (7/90-6/93)

2. Cheek, Jeffrey Mark Pulmonary
Pulmonary epithelial injury by tobacco smoke in vitro
$70,000 (7/90-6/92)

3. Davis, Paul Andrew Cardiovascular
Smoking and atherosclerosis—an autoimmune phenomenon?
$151,149 (7/90-6/92)

4. Dubick, Michael Cardiovascular
Nicotine, hypertension & induction of aortic disease
$182,010 (7/90-6/93)

5. Gershwin, Laurel Pulmonary
Effects of environmental tobacco smoke on pulmonary allergy
75,000 (7/91-6/92)

6. Gold, Ellen B. Epidemiology
Smoking and adverse reproductive health effects in women
$552,830 (7/90-6/93)

7. Gold, Ellen B. Epidemiology
Smoking effects on maternal folate and reproductive outcomes
$105,988 (7/90-6/92)

8. He, Pingnian Cardiovascular
Endothelial barrier injury by tobacco smoke
$60,945 (7/90-6/92)

9. Joad, Jesse P. Pulmonary
Sidestream smoke effects on immature airway receptors
$211,744 (7/90-6/93)

10. Joad, Jesse P. Pulmonary
Adenosine airway reactivity & receptors in smokers
$93,500 (7/90-6/92)

11. Kraegel, Susan Cancer
Analysis of ras mutations in the canine smoking model
$70,000 (7/90-6/92)

12. Last, Jerold Pulmonary
Pathogenesis of cigarette smoke-induced bronchitis
$487,719 (7/90-6/93)

13. Leung, Patrick Cancer
Tumor specific antibodies
$225,000 (7/91-6/94)

14. Oreffo, Victor Cancer
Molecular studies of nnk-induced lung tumors in hamsters
$70,000 (7/91-6/93)

15. Pinkerton, Kent E. Pulmonary
Passive smoking & clara cell development in the lungs
$435,023 (7/90-6/93)

16. Powell, Jerry Cardiovascular
Angiotensin II and restenosis after coronary angioplasty
$228,013 (7/91-6/94)

17. Robinson, Cynthia B. Cancer
Cigarette smoke induced changes in gene expression
$222,049 (7/90-6/93)

18. R
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Lung
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Nicc

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Nicc
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Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

18. Roth, Alan — Cancer
Lung cancer associated retinopathy
$352,945 (7/90-6/93)

19. Rucker, Robert B. — Pulmonary
Tobacco smoke: mechanistic roles in copd
$250,297 (7/90-6/93)

20. Rutledge, John — Cardiovascular
Effect of cigarette smoke on vascular wall permeability
$99,857 (7/91-6/92)

21. Schelegle, Edward — Pulmonary
Lung reflexes and afferent properties in health and diseases
$70,000 (7/90-6/92)

22. Stebbins, Charles L. — Cardiovascular
Nicotine & cardiovascular control during exercise
$220,346 (7/90-6/93)

23. Villablanca, Amparo — Cardiovascular
Nicotine effects on endothelial cell growth and function
$69,038 (7/90-6/92)

AWARD # 1RT-431 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Ann C. Bonham, Ph.D.

INSTITUTION University of California, Davis

TITLE OF PROJECT "CNS PROCESSING OF LUNG AFFERENT & CIGARETTE SMOKE INPUTS"

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Acute inhalation of cigarette smoke elicits immediate changes in breathing, blood pressure, and heart rate. These changes represent the body's attempt to protect the lungs by quickly expelling the noxious agent (by breathing rapidly and shallowly), and to prevent distribution of the noxious agent throughout the circulation (by decreasing blood pressure and heart rate). These complex changes are initiated in part, by stimulation of bronchopulmonary C fiber endings that are located in the lungs and bronchi that and are known to be stimulated by cigarette smoke inhalation. When exposed to cigarette smoke, the endings send signals via nerves to brain cells, however, we do not yet know where and how this sensory information is transmitted and transformed in the brain to elicit the changes in breathing, i.e., rapid shallow breathing. This research proposes to identify the pathway in the brain for smoke-induced reflex changes in breathing, blood pressure and heart. Thus far, we have injected a chemical, phenyldiguanide, in the pulmonary circulation to mimic the reflex produced by exposure to cigarette smoke. We have located a discrete region in the dorsomedial medulla which contains a small group of neurons that receive input from the bronchopulmonary C fiber endings and are required for production of the defense-like responses to bronchopulmonary C fiber excitation, i.e., rapid shallow breathing, a decrease in blood pressure, and a decrease in heart rate. In recent studies, we have further traced this pathway to neurons which modulate breathing pattern in the medulla. It appears that bronchopulmonary C fiber activation actually inhibits brain cells that enable one to inhale (inspiratory neurons) and excite cells that enable one to exhale (expiratory neurons). These findings suggest that a complex circuitry exists in the brain, whereby stimulation of endings in the lung by the environmental toxicant, cigarette smoke and in the laboratory by injecting a chemical in the pulmonary circulation actually changes breathing pattern. Understanding how and why acute exposure to cigarette smoke triggers these respiratory responses will hopefully shed light on how the brain responds to this noxious agent.

AWARD # FT - 69 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Jeffrey H. Cheek, Ph.D.

INSTITUTION UC - Davis

TITLE OF PROJECT Pulmonary epithelial injury by tobacco smoke in vitro

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Tobacco smoke is a complex mixture of toxic and carcinogenic compounds. The lung, and in particular the cells which line the conducting airways and gas exchange surfaces (i.e., pulmonary epithelium), is the primary target tissue injured by inhalation of tobacco smoke. Detailed studies of early tobacco smoke injury to pulmonary epithelium are limited by both the diversity of inhaled toxicants and the complex anatomical and cellular heterogeneity of the adult mammalian lung. Investigations of how tobacco smoke impairs pulmonary cell function thus require the development of simpler in vitro models, using defined conditions to determine the response of different lung cells to various toxicants. The purpose of this work is to develop a cell culture system to facilitate studies of relevant dosimetry and mechanisms by which specific compounds in tobacco smoke produce epithelial cell injury in the lung.

We have utilized monolayers of primary cultured alveolar epithelial (type II) cells, isolated from rat lungs, to study pulmonary cell biology in vitro and its relationship to epithelial barrier function and xenobiotic metabolizing capabilities. These monolayers develop high electrical resistances and exhibit active and passive transport characteristics representative of the pulmonary air-blood barrier in vivo. We have developed a serum-free, defined culture medium which improves the maintenance of monolayer barrier properties and other aspects of cellular function (preservation of secretory protein content and cytoskeletal structural elements). When these monolayers are exposed to ozone, an environmentally relevant air pollutant similar to oxidant compounds present in tobacco smoke, electrical resistance decreases and the permeabilities of solutes and water increases, which may explain in part the compromised air-blood barrier function occasionally seen in tobacco smoke-induced injury. Current studies are ongoing to determine relevant dosimetry and possible synergistic relationships with other components of tobacco smoke.

We are also employing biochemical methods to gain insight into relative differences in pulmonary cell susceptibility to tobacco smoke. Analyses of antioxidant enzyme activities and cellular reducing equivalents (e.g., glutathione) of freshly isolated type II cells are being compared to those in cultured monolayers to determine if increased oxidant-induced injury is inversely related to cellular antioxidant defenses. This approach will enable us to define critical differences between target and nontarget cells and provide insight into potential methods to ameliorate cellular injury resulting from exposure to tobacco smoke.

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Source: https://www.industrydocuments.ucsf.edu/docs/ltvl0000

PRINCIPAL INVESTIGATOR Paul A. Bowes, Ph.D.

CAMPUS/INSTITUTION University of California at Davis

AWARD # [illegible] AWARD PERIOD 1990-1992

TITLE OF PROJECT Smoking and Atherosclerosis--an autoimmune phenomenon?

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 7".

Smokers are known to be at an increased risk for heart disease, and it is possible that this risk may be due in part to an increased oxidative damage. Low density lipoprotein (LDL) that has been oxidized has been found in atherosclerotic plaques, and is picked up more readily by the macrophages found in areas of plaque, via the scavenger receptor. Smokers may be at an increased risk as a result of their being exposed to the oxidizing effects of cigarette smoke. There is also indication that this oxidized LDL (oxLDL) may be immunogenic and result in autoantibodies which could also play a role in plaque formation, which contains immune cells.

This project is studying the effects of smoke exposure on LDL to determine whether increased oxidation is taking place. We are also measuring for autoantibodies against oxLDL, in plasma of smokers compared to nonsmokers. We have developed the techniques necessary to isolate and oxidize LDL, and to measure the amount of peroxidative damage that has taken place. We have also obtained several monoclonal antibodies against oxLDL, against the apoB portion of LDL, and against the LDL particle itself, all of which we are presently using to characterize the LDL from smokers and nonsmokers. An immune assay has been developed to measure the autoantibodies in the plasma of smokers compared to nonsmokers, and we are in the process of making the technique more sensitive, before we begin screening the plasmas. We have also done gel electrophoresis and SDS electrophoresis along with immunoblotting of these gels to begin to characterize the LDL found in smokers, compared to nonsmokers and compare it to copper oxidized LDL.

AWARD # IRT 417 AWARD PERIOD July 1, 1990-June 30, 1993

PRINCIPAL INVESTIGATOR Michael Dubick, PhD; Carl L. Keen, PhD

INSTITUTION University of California, Davis

TITLE OF PROJECT Nicotine, Hypertension and Induction of Aortic Disease

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cigarette smoking and its major pharmacological principal, nicotine, as well as hypertension, are well recognized risk factors in the etiology of atherosclerotic vascular disease. The mechanisms which link them to disease, however, are not well understood. Recently it has been suggested that excessive concentrations of the enzyme elastase, and excessive generation of oxygen free radicals, may be involved in the development of vascular disease. Three goals of the current research are to: 1) obtain evidence for the idea that increases in elastase activity and free radical concentrations lead to vascular disease, 2) determine if cigarette smoke and hypertension contribute to increases in the above destructive factors, and 3) determine if their effects are synergistic. During the past year we have made considerable progress towards the above goals. First we have shown that aortic tissue obtained from patients with aortic aneurysmal or occlusive disease is characterized by high concentrations of iron, lipid peroxides and elastase activity compared to control tissue obtained from traffic accident victims. Second, we have shown that nicotine when given by tablet results in some, but not all of the typical tobacco smoke-induced alterations in the antioxidant defense system. Thus factors in tobacco smoke in addition to nicotine must be involved in the induction of these changes, or alternatively the nicotine must be acting synergistically with other risk factors such as hypertension.

AWARD # IRT 480 AWARD PERIOD 1990-1993

PRINCIPAL INVESTIGATOR Ellen B. Gold

INSTITUTION University of California, Davis

TITLE OF PROJECT Smoking and Adverse Reproductive Health Effects in Women

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project's main objective is to determine if cigarette smoking and passive exposure to cigarette smoke affect risk of infertility in women. Subjects, urine samples and data previously collected in a longitudinal study of female employees in the semiconductor industry are being used. That 3-year study includes 6 plants from 4 semiconductor companies. Women aged 18-44 who manufacture silicon wafers and a sample of women who work in non-manufacturing positions (N=430) are being followed prospectively. They were interviewed in-person in detail at baseline and were asked to keep daily diaries (about their habits and personal and work exposures), collect first morning urine daily, and respond to brief monthly telephone questionnaires (to determine changes in work activities or other exposures) for 6 months.

In the current project, we are using data obtained from the interviews and diaries on cigarette smoking and exposure to passive cigarette smoke, as well as on factors which may confound or modify their effects, eg, age, ethnicity, education, parity, work exposures, physical activity, stress, and alcohol and caffeine consumption. Urine samples are analyzed for cotinine, a metabolite of nicotine, to validate the self-reported smoking data. Incidence rates of anovulation (failure to ovulate), menstrual cycle abnormalities, and short fertile periods (which may be related to inability to conceive) will be studied in active and passive smokers and compared to nonsmokers by measuring hormones or their metabolites in the urine, such as pregnanediol-3-glucuronide (PdG), a metabolite of progesterone, as well as estrogen metabolites and other hormones. These rates will be adjusted for the effects of confounding factors.

Thus far, 591 cycles from 201 women have been analyzed for PdG. Of these, 51 (25%) women have had at least one anovulatory cycle. We will continue these analyses and during the next year will evaluate the relationship to smoking.

AWARD # 1RT 488 AWARD PERIOD 1990-1994

PRINCIPAL INVESTIGATOR Ellen B. Gold

INSTITUTION University of California, Davis

TITLE OF PROJECT Smoking Effects on Maternal Folate and Reproductive Outcomes

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to determine if active or passive exposure to cigarette smoke results in lower levels of the vitamin folate in the blood and affects any relationship between folate and early pregnancy loss. Folate is a vitamin that is critical to normal cell division; thus, low folate levels may increase the risk of pregnancy loss, and smoking is believed to lower folate levels. In the first phase of this study, 430 women who were enrolled in a prospective follow-up study of semiconductor workers, were asked to complete a food frequency questionnaire to assess their intake of folate. They were also interviewed in-person in detail at baseline and were asked to keep daily diaries about their habits and exposures, collect first morning urine daily (which will be assayed to detect conception and early pregnancy loss), and respond to brief monthly telephone questionnaires (to determine changes in work or exposures) for 6 months. These data will be used to determine if folate intake is related to early pregnancy loss and if this relationship is modified by smoking.

In the second phase of this study, an additional 250 similar women who work in the semiconductor industry will be asked to answer similar questions and to provide a blood sample, which will be analyzed for folate. These women will be paid for their participation and will also receive information about the adequacy of their reported dietary intake and their cholesterol and hematocrit, if they desire. This portion of the study will determine how well self-reported dietary intake of folate is reflected in blood levels and will determine the effect of active or passive smoking exposure on levels of folate in the blood. We also hope to follow some of these women to detect early pregnancy loss.

Thus far, 303 dietary questionnaires have been sent to women in the first phase, 250 (82%) of which have been completed. In the second phase, the first 180 women have been selected and are being scheduled for interviews and blood draws, which will occur soon.

2023471110

AWARD # FT 13 AWARD PERIOD 2 years

PRINCIPAL INVESTIGATOR He, Ping Kian

INSTITUTION University of California, Davis

TITLE OF PROJECT Endothelial Barrier Injury by Tobacco Smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

An increase in permeability of the endothelial barrier lining the walls of blood vessels is thought to be one of the initiating events of many diseases which include atherosclerosis, pulmonary edema, etc. Recent studies indicated that the products of tobacco smoke extract increase the permeability of cultured endothelial cell monolayers by calcium dependent processes (J. Appl. Physiol. 66:450-57,89). The objective of my research was to investigate the calcium dependent mechanisms of injury to endothelial barrier. The hypothesis which I have been testing is that calcium entry into endothelial cells, which elicits an increase in permeability, is modulated by the endothelial cell membrane potential. The membrane potential of the cells in microvessel wall was changed by altering the external potassium concentration. The corresponding changes in cytoplasmic calcium concentration, $[Ca^{++}]_i$, was measured after loading the cells forming the microvessel wall with the calcium sensitive fluorescent indicator fura-2 and permeability was measured as hydraulic conductivity, Lp. We have found calcium ionophores cause a two phase increase in permeability and $[Ca^{++}]_i$ in microvessels, which is similar to that induced by the tobacco smoke extract. In the presence of Ca^{++} ionophores, the magnitude of the initial changes in Lp and $[Ca^{++}]_i$ was attenuated by depolarizing the cell membrane in the vessel wall using high potassium (57.9 mM) Ringer's solutions. In contrast, hyperpolarizing the membrane using low potassium (0.1 mM) Ringer's solution potentiated calcium influx and the initial increase in Lp. These results conform to the hypothesis that the membrane potential modulates calcium influx into endothelial cell. The initial calcium ion influx modulates the initial increase in microvessel permeability. To investigate the more general application of this idea, we tested this hypotheses with another high permeability state, caused by removal of albumin from the perfusate (Ringer perfusion). The magnitude of changes in $[Ca^{++}]_i$ and Lp were also attenuated by depolarizing solutions. These observations indicate that membrane depolarization which reduces the driving force for Ca^{++} entry, decreases Ca^{++} influx, and attenuates the permeability changes in the high permeability states. Conversely, hyperpolarization of endothelial cell membrane, increases the driving force for Ca^{++} entry, increases Ca^{++} influx and potentiates the inflammatory response. The same mechanisms are expected to modulate injury to endothelial barrier.

AWARD # RT055 AWARD PERIOD 7/1/90 - 6/30/92

PRINCIPAL INVESTIGATOR Jesse P. Joad, M.D.

INSTITUTION University of California, Davis

TITLE OF PROJECT Adenosine Airway Reactivity and Receptors in Smokers

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Adenosine is a naturally occurring substance which causes airway obstruction at much lower concentrations when breathed by smokers and asthmatics than in normal persons. This study was designed to evaluate whether airway adenosine receptors in smokers whose airways are more reactive to adenosine differ from those in smokers less reactive to adenosine, and to determine if two drugs used to treat asthma, theophylline and cromolyn, can function in smokers' airways by blocking adenosine receptors. This year we have obtained lung tissue from 16 patients who went to surgery of whom 6 were former smokers and 5 were present smokers. Preliminary studies suggest that there may be two adenosine receptor sites; one seems to be the A_2 subtype which was expected, the other might be the A_1 subtype or it might be an artifact. There are very few of the A_2 receptors. We have also shown that stimulation of these A_2 receptors results in the expected increase in the "second messenger", cAMP. We expected theophylline and cromolyn to inhibit this increase in cAMP by blocking the receptor but so far have been unable to show that this is the case.

AWARD # KT65 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Jesse P. Joad, M.D.

INSTITUTION University of California, Davis

TITLE OF PROJECT Sidestream Smoke Effects on Immature Airway Receptors

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Children exposed to environmental tobacco smoke (ETS) have increased respiratory symptoms, measurable airway obstruction, and a higher incidence of asthma. This study was designed to investigate whether rabbits exposed to ETS at a young age have airways which are more reactive to certain chemicals and if the reason for the increased reactivity is due to the airway receptors for those chemicals. This year was spent developing the ETS exposure facility, establishing the methods to measure airway reactivity in the isolated perfused lung (IPL), establishing the methodology to study lung adenosine receptors, and exploring the correct species to study. The ETS exposure facility is now complete and exposures have been performed for 3 months. It is able to generate an ETS exposure with a respirable suspended particulate (RSP) concentration of 1.00 ± 0.03 mg/m^3 and a carbon monoxide concentration of 6.48 ± 0.29 ppm which is in the higher end of relevant human exposures. In the IPL, we were able to show increased airway reactivity to one of the chemicals, methacholine, when the lungs were exposed to 1 ppm ozone for 3 hours, thus establishing our IPL methodology. We were able to describe the adenosine receptor in lung tissue. Finally, we have decided to study developing rats rather than rabbits since our initial experience with rabbits suggested they were more expensive and harder to maintain, and because the other ETS investigators at UCD are studying rats.

AWARD # 1FT 73 AWARD PERIOD 7/1/90 - 6/30/92

PRINCIPAL INVESTIGATOR Susan Kraegel

INSTITUTION University of California, Davis

TITLE OF PROJECT Analysis of *ras* mutations in the canine smoking model

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The K-*ras* proto-oncogene codes for the K-*ras* protein in normal cells. The exact function of this protein is not known, but it probably plays a basic role in normal cell development or function. Mutations in the K-*ras* gene at one of three points results in an altered K-*ras* protein that contributes to the development and/or progression of cancer in humans and other animals. K-*ras* point mutations are reported to occur in one-third of lung adenocarcinoma specimens in people. Smoking, through the direct action of carcinogenic ingredients of tobacco smoke, may be the major causative factor in the induction of these K-*ras* point mutations based on the absence of K-*ras* activation in the lung adenocarcinomas of non-smokers. The objective of this project is to determine the role of K-*ras* oncogene changes in canine lung cancer development as a model of human lung carcinogenesis.

The first phase of this project was to examine the normal canine K-*ras* gene. Using innovative molecular technology, we determined the coding sequence of the normal beagle K-*ras* gene from positions 9 through 210. Although differences between the dog and human gene sequences occurred, the resultant dog and human K-*ras* proteins were identical in the regions studied. These results confirmed the evolutionary conservation of the K-*ras* gene.

Having established the normal or wild-type sequence, we then investigated the frequency of K-*ras* mutations in spontaneous canine lung carcinomas from biopsy specimens collected at the Veterinary Medical Teaching Hospital. Cancer causing mutations were detected in 8 of the 21 tumors examined. The frequency of K-ras mutations in dog lung cancer appears to be similar to the frequency in human lung cancer and suggests that K-*ras* gene mutations may play a similar role in canine and human lung cancer.

2023471111

Source: https://www.industrydocuments.ucsf.edu/docs/mfb0068

AWARD # RT440 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR LAST, JEROLD A.

INSTITUTION UC Davis

TITLE OF PROJECT Pathogenesis of Cigarette Smoke-Induced Bronchitis

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

We are exposing cells derived from human airway surface epithelium to environmental tobacco smoke ("sidestream smoke", smoke analagous to that inhaled from "passive smoking" of someone else's cigarettes) in a special facility designed for this purpose. In this first year of our project, we have been developing and validating appropriate assays to study the effects of smoke exposure on these cells. We have done dose-response curves for exposed cells, finding conditions that slightly and strongly effect the ability of these cells to grow and reproduce. Another aspect of this project is to determine the role of what are called heat stress proteins in protection of cells from injury by cigarette smoke. We have observed increased synthesis of this class of proteins in exposed cells and are presently designing experiments to correlate extent of injury with induction of heat stress proteins in cells exposed to various doses of smoke. Our overall objective in this study is to better understand how airway cells are injured and the normal mechanisms of protection of these cells from cigarette smoke-induced injury so as to better evaluate the risks associated with exposure to environmental tobacco smoke.

AWARD # RT 442 AWARD PERIOD 07/01/90 - 06/30/91 Ans'd

PRINCIPAL INVESTIGATOR Kent E. Pinkerton, Ph.D.

INSTITUTION University of California, Davis

TITLE OF PROJECT Passive smoking & Clara cell development in the lungs

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this work is to examine the effects of exposure to well-characterized environmental tobacco smoke (ETS) on the development of the nonciliated bronchiolar epithelial (Clara) cell in the newborn rat. The hypothesis to be tested is that ETS impairs the ultrastructural maturation and enzymatic expression of Clara cells in the perinatal lung. Pregnant rats have been exposed to ETS for 6 hours per day from day 3 through day 21 of gestation. ETS effects on litter size, body weight, lung volume and airway epithelial Clara cell development are currently being analyzed. Neonatal rats are also being exposed to ETS from 1 day to 21 days of age and will analyzed in the same manner as those animals exposed in utero. The effects of ETS exposure on the Clara cell will be examined in animals 1, 4, 7, 14 and 21 days of age. In the first year of the study we have accomplished the following: (1) the setup of exposure chambers to sidestream cigarette smoke, (2) the generation and characterization of smoke conditions during exposure, (3) exposure of timed-pregnant rats to sidestream smoke from gestation day 3 to gestation day 21 and (4) quantitative measurements of body weight gain, lung volumes and cytodifferentiation of the Clara cell from one day of age to adult in control rats. Immunohistochemical methods to determine the distribution of cytochrome P450 positive cells in the lung airways have been developed and used to determine changes which occur with normal postnatal aging in the neonatal rat. Since little information is available concerning the effects of ETS on prenatal and perinatal lung growth and development, the information gained from this study may prove highly useful in better understanding the potential risk of ETS exposure to both the unborn and newborn infant.

AWARD # 1FT 20 AWARD PERIOD 7/1/90-6/30/92

PRINCIPAL INVESTIGATOR Victor Oreffo

INSTITUTION University of California, Davis

TITLE OF PROJECT Molecular Studies of NNK-Induced Lung Tumors in Hamsters

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Lung cancer is the type of cancer that most frequently causes death in man. There are two major classes of lung cancer: small cell (SCLC) and non-small cell (NSCLC). Knowledge of the genes that are mutated in lung cancer will provide targets for treatment (i.e. gene therapy) and perhaps allow prevention of this cancer. The objective of this project is to characterize cancer gene expression that result from exposure to tobacco smoke specific carcinogen, NNK. For this study we have used innovative molecular biology techniques. DNA from the initial cancer gene examined was the K-ras gene. Regions of the gene that are targets for carcinogen damage were sequenced and mutations have been found in 3 of 6 tumors at these positions. At this frequency of 50%, it appears that K-ras mutations are important in the cancer development due to tobacco carcinogens. Additional cancer genes to be examined are the myc gene, the RB gene, and the P53 gene. We have characterized the systems for studying these genes and are currently proceeding with the analysis of tumors.

AWARD # RT92 AWARD PERIOD July 90-June 91

PRINCIPAL INVESTIGATOR Cynthia B. Robinson, M.D.

INSTITUTION Univ of CA, Davis

TITLE OF PROJECT "Changes in TGF Aand TGF a Gene Expression

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project seeks to understand the relationship between two important growth factors and the development of abnormal airway cells in response to cigarette smoke. Squamous metaplasia of the airways is an abnormal and probably preneoplastic lesion. Squamous metaplasia results when growth (increased number of cells) and differentiation (function) are disturbed. Transforming growth factor-beta (TGF-B) has been shown to promote terminal squamous differentiation in airway cells. Transforming growth factor-alpha (TGF-A) utilizes the same receptor as epidermal growth factor (EGF)-which is required for airway cell growth. Initial results of this project confirm that cultures of airway cells secrete TGF-A and TGF-B for their community's use. (autocrine/paracrine secretion) Cultured cells are being exposed to cigarette smoke and then assayed for the expression (at a molecular level) for these two growth factors. Concurrent cultures are being assayed for their degree of abnormal growth and differentiation. The degree of deviation from normal growth and function will eventually be correlated to the interplay of TGF-A and TGF-B expression in these cultured airway cells. Only a detailed study of the production of squamous metaplasia will provide answers about how cigarette smoke induces squamous metaplasia and how that process can be halted.

2023471112

Source: https://www.industrydocuments.ucsf.edu/docs/#id=0

AWARD # RT 341 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Alan M. Roth

INSTITUTION University of California, Davis

TITLE OF PROJECT Lung Cancer Associated Retinopathy

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Neurological effects secondary to cancer are referred to as 'Paraneoplastic Phenomena' and involve a wide variety of the central nervous system influencing the brain, muscle movement and vision. Small Cell Carcinoma of the Lung (SCCL), commonly associated with tobacco smoking, is the neoplasia most often associated with paraneoplastic phenomena. Several published reports describe rapid vision loss as secondary effects associated with SCCL now know as 'Cancer Associated Retinopathy (CAR)'. The biological mechanisms involved in this form of vision loss are not understood and could be either poisoning of the retina from release of soluble toxic cancer products and/or immunological reactions involving 'Antigenic Mimicry' when the immune system, responding to cancer antigens, cannot differentiate between a cancer component and an antigenically similar epitope located in the neurosensory retina. We have examined serum antibodies from a collection of CAR patients and found unusual concentrations of antibodies reactive with a small molecular weight retinal protein. In the first year we have (1) isolated the antigen from retina and protein sequencing it; (2) isolated the gene which encodes for the retina antigen and by nucleic acid sequencing are identifying the molecule; (3) investigated the extent of disease specificity of the CAR reaction in a series of CAR patients; (4) identified the site of antibody binding in the retina and (5) initiated sensitization studies in guinea pigs and rats.

Preliminary studies have shown that the gene product, the recombinant CAR antigen, is interactive only with antibodies from CAR patients and not with antibodies from patients with other forms of retinopathies such as retinitis pigmentosa and diabetic retinopathy. If we encounter an acceptable correlation between positive reactors and CAR, the test may then be considered useful in screening susceptible populations for early evidence of small cell carcinoma of the lung.

AWARD # 453 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Robert B. Rucker, PhD

INSTITUTION University of California, Davis

TITLE OF PROJECT Tobacco Smoke: Mechanistic Roles in COPD

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

A number of factors modulate the functional activities of enzymes that are involved in extracellular matrix processing. For example, lysyl oxidase, an enzyme involved in collagen and elastin crosslinking, is inhibited by oxidants and hydrophobic amines. At critical periods in lung development or lung tissue repair, the inhibition of lysyl oxidase functional activity can be very important. Normal crosslinking of collagen and elastin protects from inappropriate proteolysis by non-collagenolytic and elastolytic proteinases. Consequently our work in hypothesis is that cigarette smoke inhibits lysyl oxidase and decreased crosslinking renders elastin and collagen more susceptible to degradation. The methods and research activities involve: 1) animal models, 2) cells in culture, 3) chemical determination of crosslinks in collagen and elastin and 5) techniques to allow quantitative assessment of synthesis and deposition of collagen, elastin, and lysyl oxidase. Antibodies and nucleic acid probes for state-of-the-art analyses are available for such assays. We will address situations that result in a loss of elastin or poorly controlled redeposition following injury. Equipment and resources are in place to direct attention at identifying specific compounds in cigarette smoke that may inhibit lysyl oxidase. The access to excellent exposure facilities, and to collaborators who can aid with morphologic aspects of the work contributes significantly to the success of the proposal. The work represents an important extension of the proteinase-antiproteinase theory of emphysema.

AWARD # HL AWARD PERIOD 90-92

PRINCIPAL INVESTIGATOR Edward G. Schelegle, Ph.D.

INSTITUTION University of California, Davis

TITLE OF PROJECT Lung reflexes & afferents in health & disease

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

There are four neural receptors located in the lung that respond to physical and chemical stimuli and that send their signals to the central nervous system via the vagus nerve. The role that these neural receptors play in the symptoms, dyspnea, airway responsiveness and lung inflammation associated with chronic lung disease has not been determined. The objectives of this project are to investigate how chronic lung diseases and acute and chronic inhalation of airborne irritants (including cigarette smoke) influence lung regulatory and protective mechanisms. Using a technique to selectively block the conduction of small nonmyelinated nerve fibers (C-fibers) in dogs, we have shown that the chronic discharge of these small nerve fibers contributes to baseline breathing pattern, making it more rapid and shallow than it is in their absence. Using the same blocking technique we have begun to investigate the reflexes initiated by rapidly adapting pulmonary stretch receptors ("irritant receptors") without the confounding influence of lung C-fibers. Preliminary findings indicate that lung irritant receptors are stimulated by a decrease in lung compliance, but are not directly stimulated by histamine, a chemical stimulus previously believed to stimulate these fibers directly. Other studies underway in our laboratory indicate that indicate that chronic lung inflammation increases the baseline discharge of lung C-fibers. In combination these findings suggest that small increases in C-fiber discharge associated with chronic lung inflammatory processes could contribute to an alteration in baseline breathing pattern and that "irritant receptors" would not be expected to contribute to altered respiratory pattern until marked alterations in lung mechanics have occurred. In the coming year the effects of experimentally induced chronic lung inflammation and lung disease on the baseline discharge and reflex effects of these lung receptors will be investigated in rats.

AWARD # RT 37 AWARD PERIOD 1990-92

PRINCIPAL INVESTIGATOR Charles L. Stebbins, Ph.D.

INSTITUTION University of California, Davis

TITLE OF PROJECT Nicotine and Cardiovascular Control During Exercise

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The overall goal of this proposed research is to determine alterations in the cardiovascular response to exercise caused by nicotine in the presence and absence of coronary artery occlusion. A second goal is to examine specific mechanisms that may underlie nicotine-induced alterations in the cardiovascular response to exercise. In the last year, we have focused on the potential the relationship between nicotine and vasopressin. Nicotine stimulates the release of vasopressin which causes cardiovascular responses that are similar to those of nicotine and, as such, may contribute to the overall nicotine effect. Since vasopressin is released into the systemic circulation during exercise, we tested the hypothesis that this peptide contributes to the blood pressure response during treadmill exercise in the pig. Six minipigs were instrumented with epicardial ECG leads and venous, aortic and left atrial catheters for assessment of arterial blood pressure and heart rate and injection of radioactive microspheres for measurement of regional blood flow. All measurements were made at rest and during exercise. At a work intensity of 80% of each animal's maximal heart rate (HR) reserve, exercise-induced increases in systolic (SBP), diastolic (DBP) and mean (MAP) blood pressure, HR, rate pressure product (RPP), and regional blood flow were measured. On a separate day the workload performed by each animal was replicated in the presence of vasopressin V_1 receptor blockade using a highly specific V_1 antagonist, $d(CH_2)_5Tyr(Me)$ arginine-vasopressin (10-12 $\mu g/kg$, iv). During V_1 blockade SBP, RPP and HR were unchanged when compared to unblocked conditions. However, DBP and MAP were attenuated significantly. In addition, exercise blood flow was unchanged in skeletal muscle decreased in the spleen and increased in the stomach, small intestine, colon, pancreas, and skin. These data suggest that vasopressin contributes to the pressor response to dynamic exercise. This effect is most likely due to the peptide's vasoconstrictor action in the skin and gastrointestinal tract and is mediated by a vasopressin V_1 receptor mechanism. Because nicotine is a strong stimulus for the release of this peptide, it likely evokes increases in plasma levels of vasopressin that may result in augmented pressor response to dynamic exercise.

2023471113

Source: https://www.industrydocuments.ucsf.edu/docs/jvln0000

Grant Awards by Institution

AWARD # 1FT-72 AWARD PERIOD 7-1-90 to 6-30-92

PRINCIPAL INVESTIGATOR Amparo C. Villablanca, M.D.

INSTITUTION University of California - Davis

TITLE OF PROJECT Nicotine Effects on Endothelial Cell Growth and Function

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

ABSTRACT

Atherosclerosis (narrowing or blockage of arteries) accounts for approximately half a million deaths per year in the U.S. and is thought to be in large part a response to injury to the endothelium (the lining of blood vessels). Several factors are known to predispose to atherosclerosis including smoking. Nicotine (a major component of cigarette smoke) has been postulated to be of significant importance in the process of atherosclerosis. We wished to determine whether nicotine injured endothelial cells (cells that form the lining of blood vessels) by incubating these cells in culture with nicotine. Our results showed that nicotine increased DNA synthesis by producing injury to DNA (the genetic material) of endothelial cells. This was observed at concentration up to 10,000 times lower than would be found in blood after smoking 1-10 cigarettes. The increase in DNA synthesis represented repair of DNA. In addition, high doses of nicotine killed endothelial cells. However, very low doses of nicotine stimulated cells to divide and proliferate - a process necessary for the healing of blood vessel injury. Serum (a major component of blood), but not plasma or insulin (a blood hormone), enhanced the ability of nicotine to stimulate DNA synthesis. This suggests that factors in platelets (the cells in blood that are responsible for producing growth factors and making blood clot) are important in modulating the effects of nicotine. Our findings are the first report of direct injury and growth of endothelial cells in culture as a result of nicotine and may provide a link at the cellular level between smoking and atherosclerosis.

2023471114

University of California, Irvine

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

12 $3,753,352

b) The subject of research grants by academic discipline:

Cancer	= 2
Engineering	= 1
Epidemiology	= 1
General Biomedical Science	= 2
Public Health, Public Policy, and Economics	= 1
Pulmonary Disease	= 5

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

7 $2,825,030

g) The number and species of animals used in research:

Ferrets	= 80/year
Hamsters	= 50/year
Mice	= 340/year
Rats	= 1,070/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

3 $1,285,662

Grant Recipient(s):

1. Casey, Graham — Cancer
Involvement of the tumor suppressor gene p53 in lung cancer
$124,541 (7/90-6/92)

2. Duckles, Sue — Gen Biomed
Vascular effects of nicotine: effect of age
$331,124 (7/91-6/94)

3. Dunn-Rankin, Derek — Engineering
Optical particle size measurements of tobacco smoke
103,468 (7/90-6/93)

4. Kikkawa, Yutaka — Pulmonary
Pulmonary benzo(a)pyrene metabolism & tobacco smoking
$303,996 (7/90-6/93)

5. Osann, Kathryn E. — Epidemiology
Smoking-related risks for small cell lung cancer in women
$214,066 (7/90-6/93)

6. Pechmann, Cornelia — Pub Health
Smoking-related advertising and preteens' social perceptions
$72,837 (7/91-6/92)

7. Phalen, Robert — Gen Biomed
Doses to target tissues from inhaled tobacco smoke
$413,410 (7/90-6/93)

8. Rasmussen, Ronald E. — Pulmonary
Environmental tobacco smoke & lung development
$512,031 (7/90-6/93)

9. Selsted, Michael — Pulmonary
Smoking-induced impairment of pulmonary host defense
$381,970 (7/91-6/94)

10. Stanbridge, Eric J. — Cancer
Tumor suppressor genes in human lung cancer
$319,060 (7/90-6/93)

11. Williams, James H. — Pulmonary
Pulmonary vascular leukocytes & tobacco products
$435,721 (7/90-6/93)

12. Wong, Corinne G. — Pulmonary
Protection of lung epithelium by heat shock proteins
$541,128 (7/90-6/93)

2023471115

Source: https://www.industrydocuments.ucsf.edu/docs/lvl0000

AWARD # TRD-1RT143 AWARD PERIOD 7/1/90- 6/30/91

PRINCIPAL INVESTIGATOR Graham Casey, Ph.D.

INSTITUTION University of California Irvine

TITLE OF PROJECT Involvement of the Tumor Suppressor Gene p53 in Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

If any progress is to be made in the diagnosis and treatment of lung cancer, a better understanding of the etiologic factors involved in its development is needed. Recent experimental evidence points to the fact that common cancers arise in part from the accumulation of somatic mutations in normal genes, including the inactivation of tumor suppressor genes. The tumor suppressor gene, p53 has been implicated in the development of many malignancies, and is frequently inactivated by single nucleotide base mutations. Mutations have been detected in DNA derived from several different tumor types, including those of the lung. The present study of p53 mutations in lung tumors has several objectives: to confirm that p53 mutations are involved in the development of lung tumors; to estimate the frequency, nature and distribution of those mutations; to correlate p53 mutations with environmental exposure; and to correlate specific mutations with disease progression for prognostic purposes. To achieve these objectives, we have sucessfully applied the technique of polymerase chain reaction (PCR)-cDNA amplification and sequencing using tumor-derived mRNA from tumors samples provided by Dr. Dennis Slamon at UCLA. By establishing this technique in the laboratory we are able to analyse samples more rapidly and efficiently than was previously possible. At this time we have analysed over 40 samples, and our objective is to analyse up to 100 samples. Samples are coded, and will not be broken until sufficient samples have been analysed. Mutations have been observed in 19/41 samples (46%). They occurred at many different sites within the conserved domain of the p53 gene, consistent with observations made in other cancers. Two separate sites were mutated in at least two different tumors suggesting that there are hot-spots for mutation within this conserved domain. Interestingly, 7/19 (37%) of the mutations were G to T transitions. This mutation is consistent with those caused by benzo(a)pyrene adducts, a major product of tobacco smoke. This type of transition has rarely been reported for other tumors. Our aim for the final year is to complete our mutation analyses, and to correlate specific mutations with tumor type and disease progression.

AWARD # 1RT 232 AWARD PERIOD 7-1-90 to 6-30-93

PRINCIPAL INVESTIGATOR Derek Dunn-Rankin

INSTITUTION University of California, Irvine

TITLE OF PROJECT Optical Particle Size Measurements of Tobacco Smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

To accurately predict the deposition of cigarette smoke particles in the tracheo-bronchial tract, requires an accurate measurement of the smoke particle size as it enters the smoker's airway. This project is aimed at providing this accurate measurement. The project has three principal objectives: (1) determine the measurement technique most suitable for sizing cigarette smoke aerosols *in situ* as it leaves the cigarette, (2) construct a laboratory particle sizer based on the optimum sizing technique, and (3) measure both mainstream and sidestream smoke particle size as a function of cigarette type, puff characteristics, and the length remaining in the tobacco column (i.e., how much of the cigarette remains to be smoked).

The first part of the project compares three optical particle sizing techniques that are commonly used in combustion research for sizing small particles of soot and smoke. The techniques include a polarization ratio technique, an extinction/scattering ratio technique, and a multiple angle scattering ratio technique. All three of these optical sizing techniques can be used *in situ* and do not perturb the system under study. The experimental apparatus required to compare the techniques has been completed, and calibration experiments with mono-sized latex spheres are in progress.

In support of the experimental study, we have completed numerical codes that predict the relationship between particle size and light scattering behavior for each of the methods. Quantitative particle sizing with optical techniques is usually based on the Mie theory of light scattering assuming a collection of mono-sized spherical particles. We have found, however, that when the collection of particles has a wide size distribution, the relationship between the representative mean particle size and the light scattering behavior can be multi-valued in the size range of interest. It is important, therefore, to include size distribution effects in the theoretical treatment of optical particle sizing for cigarette smoke.

AWARD # 1RT 154 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Yutaka Kikkawa, M.D.

INSTITUTION University of California, Irvine

TITLE OF PROJECT Pulmonary Benzo(a)pyrene Metabolism and Tobacco Smoking

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Carcinogenesis of lung due to Tobacco-Smoke begins when pre-carcinogen, contained in tobacco-smoke such as benzo (a) pyrene (BP) is converted to carcinogen and binds with DNA within the lung cells.

This proposal seeks to clarify the role of two metabolic pathways in conversion of pre-carcinogen to carcinogen in different cell types of the lung.

First year of this program has been devoted to:

1) recruitment of qualified pH.D. to carry out the experiments which was successfully completed in the first half and
2) to develop and modify methodologies, specifically adaptable to this project.

Since it is anticipated that cytochrome P450 IA1, IA2 will be induced by tobacco smoke, we utilized 3-methylchorantrane (3MC) which induces the same P450 isozymes as quick means of P450 induction. We refined HPLC technique to resolve four metabolites of authentic standards. These methodologies have been applied then to 3MC-induced microsomes. This phase of study, therefore, is ready to be applied to tobacco-smoke animals. We are in the middle of developing techniques to test free-radical mediated conversion of BP.

In the meantime, we noticed that over 60% of BP metabolites are bound to tissue components of microsomes. Our study indicates that there are four distinct bands (proteins); the nature of which is under investigation. BP-protein binding may prove to be an important mechanism for modulating carcinogenesis of tobacco-smoke.

AWARD # 1 RT 34 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Kathryn E. Osann, Ph.D.

INSTITUTION University of California, Irvine

TITLE OF PROJECT Smoking-Related Risks for Small Cell Lung Cancer in Women

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Kathryn E. Osann. Smoking-Related Risks for Small Cell Lung Cancer in Women. Award # RT 34. Award period 7/1/90-6/30/93.

The objective of this study is to identify a subgroup of women smokers who are at greatly increased risk for small cell carcinoma of the lung, a disease with high mortality which appears to be increasing in California at this time. This study is investigating the importance of hormonal factors (including use of exogenous estrogens and menstrual and pregnancy histories), exposure to specific brands of cigarettes over the lifetime of the smoker, family history of cancer, and exposure to radon in homes. The study will evaluate the extent of interactions between smoking and other risk factors for small cell carcinoma of the lung in women.

The first six months of this three-year study were devoted the development and pre-testing of the questionnaire, obtaining the necessary institutional approval from hospitals, and recruitment of physicians to participate in the study. To date, the study protocol has been approved at 15 hospitals in Orange County and Long Beach and is pending approval at three additional hospitals. The first cases of small cell carcinoma were referred to the study in January, 1991. As of June 18, 1991, 38 patients have been referred to the study over a 5 month period. Fifteen patients (average age at diagnosis 61.8 years) have completed interviews. An additional 9 patients have been identified but not yet interviewed, pending return of the informed consent. Seven patients expired prior to contact, 3 patients declined to be interviewed, and 4 patients were not reachable by telephone.

The identification of controls through random-digit dialing will begin in July, 1991. Data will be analyzed after completion of all interviews.

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AWARD # 1RT-324 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Robert F. Phalen

INSTITUTION Univ. California, Irvine

TITLE OF PROJECT Doses To Target Tissues From Inhaled Tobacco Smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The overall problem to be solved is to improve the accuracy in defining the deposited doses of inhaled cigarette smoke received by non-adults and by laboratory animals. The research is focused on three specific objectives: (1) measure deposits of mainstream and sidestream cigarette smoke in hollow models that represent airways of adults and children, (2) calculate mainstream and sidestream cigarette smoke deposition doses to various tissues for various ages and various states of physical activity, (3) calculate mainstream and sidestream cigarette smoke deposition doses to various tissues of laboratory animals.

In year one we have received and checked the aerosol characterization equipment, set up a constant humidity cigarette storage system, designed and constructed a smoke dilution machine, installed the basic particle deposition software on our computer and begun a study of cigarette smoke optical and aerodynamic properties. To date no major unanticipated problems have arisen in the research. The achievements thus far indicate that the original project plan is feasible.

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/91

PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.D.

INSTITUTION University of California, Irvine

TITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The goal of this project is to determine the effects of environmental tobacco smoke (ETS) in the developing lung. The rationale for the study is that young children may be exposed to relatively high indoor concentrations of tobacco smoke and possibly other pollutants. An animal model, the juvenile ferret, is being used in this study. The lung of this species resembles that of the human more than do the lungs of other commonly used laboratory animals. The ferrets are being exposed to ETS acutely or chronically during development, and the effects on lung structure quantified by microscopy of tissue sections. In the first year of this study cigarette smoking machines, exposure apparatus and smoke generation and measurement methods were installed. Acute exposure dose-response experiments (1 hr/day, 3 days, 30-80 mg smoke particles/m^3) with 4-week-old kits indicated no immediate severe effects. Total numbers of cells recovered in lung washings were slightly increased and microscopic examination indicated increased cell proliferation in the smoke exposed animals. Experiments involving longer exposure to higher smoke concentrations have been completed and tissue samples are being analyzed. Tentative conclusions are (1) the juvenile ferret tolerates the handling and smoke exposure methods very well and is a useful species for the study of effects of air pollutants in the lung; (2) acute effects of exposure to ETS are not severe, but they can be detected and quantified. The major goal for the second year will be to determine the effects of daily exposure to ETS during the period of development from 5 weeks to 20 weeks of age.

AWARD # 1RT 236 AWARD PERIOD 07/01/90-06/30/91

PRINCIPAL INVESTIGATOR Eric J. Stanbridge, Ph.D.

INSTITUTION Microbiology and Molecular Genetics

TITLE OF PROJECT Tumor Suppressor Genes in Human Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Eight human non-small cell (NSC) lung cancer lines were analyzed for p53 expression. Northern and western blot analysis showed wide variation in p53 expression allowing to distinguish cell lines: A) positive for mRNA and negative for protein (A549 and A427 cells); B) (+) for mRNA and protein (B39TL, TBE and SW1271); C) (-) for mRNA and protein (Calu6 and Hut292DM); and D) (+) for protein but with barely detectable levels of mRNA (A431).

To evaluate the role of p53 anomalies detected in these lung cancer cells, transfection experiments were initiated using both wild type and mutant forms of p53 cDNA, under transcriptional control of a CMV constitutive promoter. Preliminary results indicate that transfection of mt p53 appears to confer a growth advantage to Hut292DM and B39TL cells whereas wt p53 is without effect.

To analyze the potential growth inhibitory effect of wt p53 in candidate lung cancer cells, we also have subcloned the wt p53 cDNA under transcriptional control of an inducible SV40-lacZ hybrid promoter. Experiments are currently underway to evaluate the effect of conditional wt p53 expression on cellular proliferation of tumor cells cotransfected by this p53-lacZ promoter construct together with the corresponding lacI repressor construct.

AWARD # 1 RT 224 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR James H. Williams, Jr., M.D.

INSTITUTION University of California, Irvine

TITLE OF PROJECT Pulmonary Vascular Leukocytes and Tobacco Products

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this project is to examine the potential role of inflammatory blood cells trapped within the vessels of the lung (pulmonary vascular leukocytes) in the development of emphysema associated with tobacco inhalation and nicotine injection, and to examine means of possibly modifying these processes. This report reflects the first ten months of this three year project.

In initial experiments with a rat model, we were unable to detect an effect of nicotine injections on pulmonary vascular leukocytes, although others had reported stimulation of circulating blood cells in rats injected with nicotine. Because pathologic review of the lungs suggested that we were recovering only 30-50% of the leukocytes, we sought to improve our harvesting technique, and potentially improve our ability to detect mild degrees of cell accumulation. After examining a wide range of modifications, we increased the yield to approximately 70%.

We then examined the effects of a bacterial wall component (endotoxin), which has also been reported to induce emphysema, and which is known to produce severe inflammation in the lung, in order to be confident that our improved methods could detect the inflammatory response in the lung. We found a 5-10-fold increase in the number of leukocytes which could be recovered from the lung following endotoxin, particularly of neutrophils, which are thought to play a role in emphysema. This increase in leukocyte numbers was associated with an increase in the adhesive properties of these cells, suggesting a mechanism by which they may accumulate. In addition, these cells tended to release more oxygen radicals upon stimulation, which may contribute to lung injury, including emphysema.

We then examined the effects of tobacco inhalation on rats, and found acute tobacco exposure also increased recovery of pulmonary vascular leukocytes, although to a much milder degree. Further, these cells tended to be more adherent and to release more oxygen radicals following stimulation, consistent with a role of these cells in emphysematous lung injury. These experiments are currently being extended to examine longer exposure, other species, and other potential mediators of lung inflammation and injury, and to characterize the physiologic sequelae of these events.

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AWARD # 223 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Cerimwa Wong, Ph.D.

INSTITUTION University of California, Irvine

TITLE OF PROJECT Protection of Lung Epithelium by Heat Shock Proteins

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Statistics released by the Department of Health and Human Services demonstrate that smoking causes more premature deaths than cocaine, heroin, alcohol, fire, automobile accidents, homicide, and suicide combined. These numbers indicate the continued resistance of a significant fraction of the population to quit smoking despite common knowledge of health hazards. The research objective of this project is to define cellular protective mechanisms for promoting and enhancing survivability of the lung epithelium. Currently, the protective responses of lung epithelial cells to tobacco-specific toxins and subsequent cellular damage are poorly understood. Thus, the proposed studies seek to define whether stress proteins can provide protective effects against a variety of traumatic events.

Thus far, in this past year, studies support the primary hypothesis that "stress proteins" are either induced or elevated from nonstructive levels in cultured human lung epithelial cells after exposure to tobacco-specific compounds such as nicotine derivatives. Such stress proteins (SPs) belong to a family(ies) of proteins either induced or synthesized at higher levels in cells after treatment with toxic chemicals and/or exposed to adverse environmental conditions. When heat is the stressing agent, such proteins are called heat shock proteins (HSPs). These stress proteins have been shown to provide protective effects against a variety of traumatic events. Additional experiments demonstrate that similar proteins are elicited in these cultured lung cells under conditions of heat stress or shock. In parallel experiments, intracellular glutathione (GSH) levels were assessed as a quantitative index of stress after cellular exposure to selected tobacco-specific toxins. GSH functions in many vital capacities for critical maintenance and protection of cellular health so that fluctuations of GSH levels provide an indication of cellular homeostasis. The studies show that selected tobacco-specific compounds such as N-nitrosonornicotine perturb GSH levels.

Finally, experiments currently in progress will determine whether induction of such stress proteins prior to exposure of tobacco-specific compounds may protect cultured lung epithelial cells from subsequent damage by tobacco-specific compounds. Eventually, pharmacologic therapeutic approaches may be developed for enhancing survivability of the lung epithelium following chronic exposure to tobacco-specific toxins present in tobacco smoke.

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